Proposed Registration Decision PRD2012-30

Kasugamycin

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Overview

Proposed Registration Decision for Kasugamycin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Kasugamycin Technical Bactericide and Kasumin 2L Bactericide, containing the technical grade active ingredient kasugamycin, to control or suppress bacterial diseases on greenhouse and field fruiting vegetables, pome fruits and walnuts.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Kasugamycin Technical Bactericide and Kasumin 2L Bactericide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's *(a)* efficacy; *(b)* effect on host organisms in connection with which it is intended to be used; and *(c)* health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on kasugamycin, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on kasugamycin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Kasugamycin?

Kasugamycin is an aminoglycoside antibiotic that is produced by *Streptomyces kasagiensis*, which was first isolated from a soil sample collected in Nara, Japan. It prevents protein synthesis in bacterial cells.

Health Considerations

Can Approved Uses of Kasugamycin Affect Human Health?

Kasumin 2L Bactericide containing kasugamycin is unlikely to affect your health when used according to label directions.

Potential exposure to kasugamycin may occur through the diet (food and water) or when handling and applying the end-use product Kasumin 2L Bactericide. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, Kasugamycin Technical Bactericide was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was moderately irritating to the eyes; therefore, the signal word and hazard statement "WARNING – EYE IRRITANT" are required on the label. It was minimally irritating to the skin. The potential for an allergic reaction was identified and the hazard statement "POTENTIAL SENSITIZER" is required on the label.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product Kasumin 2L Bactericide was low via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin and eyes. The potential for an allergic reaction was identified and the hazard statement "POTENTIAL SENSITIZER" is required on the label.

Kasugamycin did not cause cancer in animals and did not damage genetic material. There was no indication of damage to the nervous or immune systems. Health effects in animals given repeated doses included effects on the skin at points of contact, kidneys, testes and blood. Kasugamycin did not cause birth defects in animals; however, reduced fertility was noted in males at high doses.

When kasugamycin was given to pregnant animals, minor effects on the skeleton of the developing fetus were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to kasugamycin than the adult animal.

The risk assessment protects against the effects of Kasugamycin Technical Bactericide by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants, the subpopulation which would ingest the most kasugamycin relative to body weight, are expected to be exposed to less than 3.0% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from kasugamycin is not of concern for all population sub-groups.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using kasugamycin on fruiting vegetables (CG 8-09), pome fruits (CG 11-09) and walnuts were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Risks in Residential and Other Non-Occupational Environments

Exposures of adults, youths and children, through contact with transferable residues following commercial application of kasugamycin to residential fruit trees and pick-your-own orchards, are not of concern.

The risk to individuals through contact with transferable residues following commercial application of kasugamycin on residential fruit trees (for example, apples, pears) was assessed and determined not to be of concern.

Taking into consideration label requirements that include the timing of applications and the long pre-harvest interval, the risk to adults, youth and children that enter treated orchards for "pick-your-own" activities is not of concern.

Occupational Risks From Handling Kasumin 2L Bactericide

Occupational risks are not of concern when Kasumin 2L Bactericide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Kasumin 2L Bactericide as well as field workers re-entering treated fields, nurseries and greenhouses can come in direct contact with Kasumin 2L Bactericide residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Kasumin 2L Bactericide, and during clean-up and repair, must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers do not enter treated fields, orchards, and greenhouses for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Kasugamycin Is Introduced Into the Environment?

Kasugamycin is not expected to persist in the environment and is not expected to pose a risk to wild mammals, birds, earthworms, honeybees, or aquatic organisms. A risk to terrestrial plants was identified; therefore, statements on the product label are required to inform users of the potential risks, and no-spray buffer zones (2 meters) are required during application to protect habitats downwind of the application site.

Kasugamycin enters the environment when used as a bactericide on the foliage of pome fruit trees, walnut trees and field-grown fruiting vegetables (also proposed for greenhouse fruiting vegetables). Kasumin 2L Bactericide is applied by field sprayer or airblast application and, as such, there is a potential that non-target terrestrial and aquatic habitats may be exposed to the chemical as a result of spray drift or runoff.

Once in the environment, kasugamycin is broken down by microbial activity in soil and in water/sediment systems and is expected to be slightly to moderately persistent in the environment. Kasugamycin is not volatile and is not expected to be detectable in air. Leaching to

groundwater is not expected to be a concern for either the parent compound or the transformation products. Kasugamycin is highly soluble in water and is likely to move off the treated field and enter aquatic environments. Two major transformation products, kasugamycinic acid and kasugabiosamine, are produced in water and are not expected to persist in the environment. Hydrolysis may be an important process in the transformation of kasugamycin (particularly at higher pH), while phototransformation is not considered an important route of transformation on soil or in water. In aquatic environments kasugamycin is not likely to accumulate in fish tissues.

Kasugamycin is not expected to pose risks to wild mammals, birds, earthworms, honeybees and aquatic organisms at the proposed use rates. A risk to terrestrial plants was identified; thus, to minimize the potential for exposure resulting from off-field drift, no-spray buffer zones will be required between the treated area and downwind terrestrial habitats. No environmental risk is expected from potential exposure to the major transformation products of kasugamycin.

Value Considerations

What Is the Value of Kasumin 2L Bactericide?

Kasumin 2L Bactericide is an antibiotic that controls or suppresses bacterial diseases on greenhouse and field fruiting vegetables, pome fruits and walnuts. It controls fire blight on pome fruits. Kasumin 2L Bactericide represents a valuable tool for management of bacterial diseases given the limited number of registered alternatives available as well as the resistance issues and limitations stemming from the use of streptomycin and copper.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Kasumin 2L Bactericide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Kasumin 2L Bactericide on the skin or through inhalation of spray mists, anyone mixing, loading and applying Kasumin 2L Bactericide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers not enter treated fields, orchards, and greenhouses for 12 hours after application. In addition, standard label statements to protect against drift during application were added to the label.

Environment

No-spray buffer zones of two meters are required for the protection of non-target terrestrial habitats.

Additional advisory statements on the potential for runoff of kasugamycin residues to adjacent aquatic habitats are required.

Next Steps

Before making a final registration decision on kasugamycin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

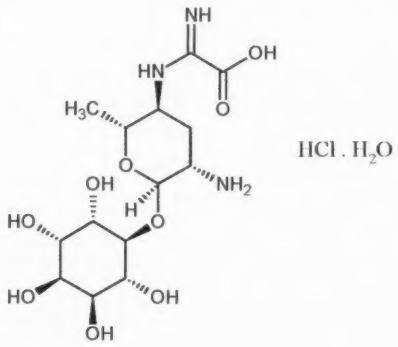
When the PMRA makes its registration decision, it will publish a Registration Decision on kasugamycin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Kasugamycin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Kasugamycin present as hydrochloride hydrate
Function	Bactericide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	[5-amino-2-methyl-6-(2,3,4,5,6-pentahydroxycyclohexyloxy)tetrahydropyran-3-yl]amino-α-iminoacetic acid hydrochloride hydrate
2. Chemical Abstracts Service (CAS)	3-*O*-[2-amino-4-[(carboxyiminomethyl)amino]-2,3,4,6-tetradeoxy-α-D-arabino-hexopyranosyl]-D-chiro-inositol monohydrochloride hydrate
CAS number	19408-46-9
Molecular formula	$C_{14}H_{25}N_3O_9 \cdot HCl \cdot H_2O$
Molecular weight	433.86
Structural formula	 $HCl \cdot H_2O$
Purity of the active ingredient	75.1%

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—Kasugamycin Technical Bactericide

Property	Result
Colour and physical state	Orange solid with tinge of brown
Odour	Odourless
Melting range	202–230°C (decomposition)
Boiling point or range	NA
Density	0.40–0.46 g/mL
Vapour pressure at 25°C	< 0.013 mPa
Henry's law constant at 20°C	2.44×10^{-13} atm·m^3·mole^{-1}
Ultraviolet (UV)-visible spectrum	Acid media (0.1N HCl): No absorbance maxima detected. Basic media (0.1N NaOH): $\lambda = 203.3$ nm , $\varepsilon_{max} = 143418$ Neutral (aq): $\lambda = 200.5$ nm, $\varepsilon_{max} = 6573.5$
Solubility in water at 25°C	pH — g/100 mL 5 — 20.7 7 — 22.8 9 — 43.8
Solubility in organic solvents at 25°C (g/100 mL)	Solvent — Solubility (g/100 mL) Methanol — 0.744 Hexane — $< 1 \times 10^{-5}$ Acetonitrile — $< 1 \times 10^{-5}$ Methylene chloride — $< 1 \times 10^{-5}$
n-Octanol–water partition coefficient (K_{ow})	pH — log K_{ow} 5 — < -1.96
Dissociation constant (pK_a)	$pK_{a1} = 3.23$ $pK_{a2} = 7.73$ $pK_{a3} = 11.0$
Stability (temperature, metal)	An aqueous solution of Kasugamycin Technical Bactericide showed a decrease of 5.3% relative a.i. conc. when held at 0°C for 47.5 hours. A similar solution showed a decrease of 32.6% when held at 54°C for 14 days. No changes in a.i. level occurred when Kasugamycin Technical Bactericide was held in contact with zinc and iron foils for 24 hours.

End-use Product—Kasumin 2L Bactericide

Property	Result
Colour	Blue-green
Odour	Faint characteristic odour
Physical state	Liquid
Formulation type	Solution
Guarantee	2.0%
Container material and description	Plastic jugs, 5, 10 and 20 L
Density	0.97–1.04 g/mL
pH of 1% dispersion in water	4.03 (1% solution)
Oxidizing or reducing action	The product was compatible with the following test reagents: distilled water, powdered iron, and monoammonium phosphate. An exothermic reaction was observed when mixed with potassium permanganate; thus contact with oxidizing agents should be avoided.
Storage stability	The product is stable for 12 months when stored in commercial packaging at ambient temperature.
Corrosion characteristics	The product is not corrosive when stored for 12 months in commercial packaging at ambient temperature.
Explodability	The product does not contain ingredients which are potentially explosive.

1.3 Directions for Use

Kasumin 2L Bactericide is to be applied preventatively as a foliar spray when conditions favour disease development. Up to three applications at 1.2 L/ha are recommended on greenhouse and field fruiting vegetables. Up to four applications at 5.0 L/ha are recommended on pome fruits and walnuts. Sufficient water volume is required to provide good coverage of treated foliage. Kasumin 2L Bactericide may be tank-mixed with certain conventional fungicides for use on greenhouse and field fruiting vegetables.

1.4 Mode of Action

Kasugamycin is an aminoglycoside antibiotic and belongs to the chemical group of hexopyranosyl antibiotics (FRAC Group 24). Kasugamycin inhibits protein synthesis by preventing the incorporation of amino acids into proteins at specific ribosome sites.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Kasugamycin Technical Bactericide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70-120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

High performance liquid chromatography with ultraviolet detection (HPLC-UV) method #Meth-146 (Revision #4), dated February 12th, 2002, was developed and proposed for data generation and enforcement purposes in plant matrices. Modified HPLC-UV methods FEQL Project No. 0407 and FEQL Project No. 0706 and modified HPLC with tandem mass spectrometry (HPLC-MS/MS) methods #Meth-146 (Revision #4 – no date reported) and #Meth-146 (Revision #4), dated July 11th, 2011, were also developed and proposed for data generation purposes in plant matrices. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the lowest limit of method validation. Acceptable recoveries (70-120%) were obtained in plant matrices. No extraction efficiency data were provided but results from plant (i.e. lettuce, rice, tomato) metabolism studies supported the use of the extraction solvents in the enforcement method to adequately release the residues of kasugamycin. No livestock analytical method was submitted.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Kasugamycin Technical Bactericide (hereinafter referred to as kasugamycin) is a wide-spectrum aminoglycoside antibiotic produced during fermentative growth of *Streptomyces kasugaensis*. Kasugamycin acts on susceptible pathogens by inhibiting the incorporation of amino acids during protein synthesis. The mode of action for kasugamycin is different than that of other aminoglycosides as it acts on an earlier step in protein synthesis to completely inhibit protein synthesis, as opposed to other aminoglycosides such as streptomycin, which cause a miscoding of amino acids.

A detailed review of the toxicological database for kasugamycin was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Some of the studies were conducted prior to the implementation of international Good Laboratory Practice guidelines; however, the majority of the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Overall, the scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to kasugamycin.

Toxicokinetic studies conducted with radiolabeled kasugamycin in rats demonstrated that absorption was low (1-4% of administered dose (AD)), rapid, and similar between sexes following either a single or repeated-dose, regardless of dose level. Excretion was similar between sexes and among dose groups with the majority of the administered radioactivity recovered within 48 hours from the feces (82-94%), and to a lesser degree from the urine (1-3%). No radioactivity was observed in the bile following biliary cannulation, indicating that the radioactivity identified in feces represented unabsorbed kasugamycin. Radiolabel was detected at elevated levels in the kidneys, urinary bladder, lymph nodes and pancreas of both sexes and liver and uterus in females shortly after dosing; however, at 168 hours post-dose, radioactivity was detectable in the kidneys only, at low levels. The metabolites identified were similar between the sexes and dose groups. Unchanged parent compound was the major component identified in the feces, urine, plasma and kidney. Minor amounts of the metabolite, kasuganobiosamine, were also identified in the urine, plasma, and kidney. In the liver, trace amounts of radioactivity revealed what was most likely unchanged parent, kasuganobiosamine, and the intermediate metabolite, kasugamycinic acid. Identified metabolites were not quantified since adequate chromatographic separation of the parent and its metabolites could not be achieved. The biotransformation pathway of kasugamycin involved deamination/oxidation of the -C=N- bond to kasugamycinic acid, followed by decarboxylation/hydrolysis to yield kasuganobiosamine.

In the rat, kasugamycin was of low acute toxicity via the oral, dermal and inhalation routes of exposure. Kasugamycin was moderately irritating to the eyes and slightly irritating to the skin of rabbits. Kasumin 2L Bactericide was also of low acute toxicity via the oral, dermal and inhalation routes of exposure in rats and was minimally irritating to the eyes and skin of rabbits. Both kasugamycin and the end-use product Kasumin 2L Bactericide were considered potential sensitizers due to their significant protein content as a result of the crude extraction method used during the production of kasugamycin.

Repeat dose studies conducted via the oral (rat, mouse and dog) and dermal (rat) routes of exposure identified the kidney as a target organ of toxicity. Testes were also a target organ in all species following oral dosing. In addition, clinical signs of toxicity, mainly associated with contact with the test substance, were noted in multiple studies. Decreases in body weight and body weight gain were also noted at high doses.

The kidney is a known target organ for aminoglycoside antibiotics. Renal effects attributed to kasugamycin were exhibited in rats and mice. In male rats, an increased incidence of eosinophilic bodies was observed in the proximal tubular cells of kidneys following short-term dietary administration of kasugamycin. A similar finding, an increase in brown pigment deposition, was noted in the proximal tubular cells of the kidneys for both sexes in the rat chronic study. Relative kidney weights were increased in both sexes following short-term and chronic oral dosing. Females in the short-term oral study did not exhibit renal histopathology; however, an increase in epithelial cells was noted in the urinary sediment at the high dose. Decreases in urinary pH were also observed in both sexes. An increased incidence of chronic progressive nephropathy and pelvic dilatation were also noted in the kidneys of F_1 males in the multigeneration reproductive toxicity study. In the repeat-dosing dermal study, tubular regeneration was also noted in the kidneys of both sexes, along with renal mineralization in females. In the mouse, diffuse basophilia and hyperplasia were noted in the tubular epithelium of the pars recta region of the kidney in females following short-term dietary administration. Although renal pathology was not observed in the dog, decreases in urinary pH and urinary volume along with increases in urinary specific gravity were evident following short-term oral dosing. Non-adverse increases in blood urea nitrogen (BUN) were also observed in the chronic dog study.

Testicular effects were noted in multiple species following treatment with kasugamycin. In the short-term mouse dietary study, an increase in the incidence and severity of tubular dilatation and degeneration was noted, along with the presence of spermatoceles. Testes weights were also increased in these animals. In the rat chronic dietary study, an increased incidence of testicular atrophy and softening as well as an increase in incidence and severity of tubular atrophy was noted in high-dose animals. In the dietary multigeneration reproductive toxicity study, parental animals from both generations exhibited testicular effects at the high-dose. In the P-generation, unilateral atrophy and/degeneration were reported in several animals. Effects were more pronounced in F_1 males. Testes were noted to be small and/or containing fluid, along with marked to severe bilateral testicular atrophy and/or degeneration, and a complete loss of germinal epithelium. In the dog, an increase in the incidence of chronic inflammation was noted in the testes of high dose animals following 12 months of dietary administration.

Irritation, associated with contact with the test substance was noted in all species following oral dosing with kasugamycin. In a short-term dietary study in the mouse, perianal reddening was noted in both sexes, with chronic inflammation and ulceration of the anus observed at a higher dose. Two high dose males and one mid-dose female were sacrificed in extremis due to extensive abrasions and/or ulcerations in the perianal/perigenital region. Similar effects were observed in high-dose rats in the dietary multigeneration reproduction study, with red and swollen skin observed around the anal opening in both sexes and generations. At necropsy, red foci/areas were noted in the rectum of P and F_1 animals, with thickening of walls of the rectum in F_1 males. Squamous cell hyperplasia was observed at the ano-rectal junction in P-generation males. Although similar effects were not observed in other rat studies, an increased incidence of nasal rhinitis was noted in high-dose males in the chronic study. In dogs, swollen mouth and tongue lesions (atrophy of dorsal epithelium, loss of epithelial papillae of the dorsal surface, serous exudate, chronic inflammation and ulceration) were noted following short-term dosing in the diet. However, these effects were not observed at a similar dose in the subsequent 12-month dietary study.

Following short-term dermal dosing, females appeared to be more susceptible to dermal irritation than males, exhibiting a greater number of effects (ulceration and encrustation) at comparable doses. There was evidence that the severity of dermal irritation increased with the duration of dosing. Acanthosis, inflammation and ulceration were noted in treated skin of both sexes at the highest dose tested. Minimal effects were also observed in one mid-dose female. A slight decrease in thymus weights were noted in mid-dose females at the lowest observed adverse effect level (LOAEL). It is unclear if alterations in thymus weights were directly attributed to treatment or were a secondary effect due to stress associated with dermal irritation. At higher doses, body weight effects, decreased spleen weights and increased incidences of tubular regeneration in the kidney were observed in both sexes, along with renal mineralization in females.

Other effects noted in the database included an increase in foam cell aggregation in the lungs of high dose rats of both sexes in the chronic study and decreases in red blood cell parameters (RBC counts, hemoglobin concentration and hematocrit) in rodents.

Kasugamycin was not genotoxic in the standard battery of in vitro and in vivo genotoxicity tests. There were no treatment-related neoplastic lesions in the rat or mouse following chronic dietary exposure.

In the dietary multigeneration reproductive toxicity study in rats, decreases in body weight and body weight gains in P-generation males were observed at the LOAEL. In addition, renal effects, testicular effects and irritation were noted at higher doses. Testicular effects contributed to reduced fertility during mating of F_1 males, with only two thirds of the high-dose F_1 males (16/24) able to sire a litter (F_{2A}). A subsequent mating confirmed that the effects on fertility were attributed to males. In addition, a 2-fold increase in pre-coital interval relative to control animals was noted during the second mating of the F_1 generation. Kasugamycin did not affect fertility or fecundity at lower doses. There were no treatment-related findings in the offspring.

The developmental toxicity of kasugamycin following gavage dosing was investigated in rats and rabbits. In rats, there was an increased incidence of shortening and/or absence of the 13th rib in fetuses at the highest dose tested. This finding was observed at a dose level that also caused toxicity in the dams, as evidenced by an increased incidence of loose stool and distention of the large intestine with stool in the cecum, and decreases in maternal body weight, body weight gains and food consumption. There was no evidence of sensitivity of the young.

In a range-finding developmental toxicity study conducted in rabbits, abortions were noted at doses of 30 mg/kg bw/day and above. Severe maternal toxicity, characterized by body weight loss, large decreases in food consumption, reduced fecal output and fluid and gaseous distention of the gastro-intestinal tract, was noted in these animals, as well as matted and stained fur. No litter data were available at doses of $\geq$ 100 mg/kg bw/day as all animals were sacrificed prior to study completion due to abortion or severe maternal toxicity. In the main study, effects noted in dams at the highest dose tested (10 mg/kg bw/day) were limited to a very slight decrease in body weight gain at initiation of dosing along with few feces and decreased food consumption sporadically throughout treatment; however, these effects were considered non-adverse due to their low magnitude and inconsistency. Abortions, which were preceded by body weight loss, were noted in two low-dose and two high-dose females; however, there was no evidence of a dose-response. Necropsy findings showed reduced and gaseous or fluid stomach, intestinal and/or cecal contents in these animals. There were no treatment-related increases in the incidence of malformations and/or variations in fetuses.

Several classes of antibiotics are well known to be toxic to the highly sensitive beneficial gut flora of the rabbit. Enterocolitis, a common occurrence in rabbits following antibiotic administration, is characterized by decreased activity, dehydration, weight loss, diarrhea or decreased feces, perianal staining and gaseous and/or fluid distention of the gastrointestinal tract, ultimately resulting in death. Disruption of the normal enteric flora, which acts as a microbial barrier, results in a proliferation of resident pathogenic bacteria. Overgrowth of *Clostridium* sp. is most commonly associated with enterocolitis following prolonged antibiotic therapy in rabbits, although *E. coli, Eimeria* sp., *Cyrpotosporidia*, or rotavirus may also be implicated. The European Medicine Agency (EMEA) noted abortions and increased resorptions, along with decreased fetal weight in a rabbit developmental toxicity study conducted with Apramycin, another aminoglycoside antibiotic. These effects were noted along with reduced food consumption and body weight gain in dams. EMEA considered the effects on the fetus as secondary to severe maternal toxicity and concluded that as rabbits are highly susceptible to the effects of antibiotics on their gut flora, the rabbit is not a suitable species for developmental toxicity studies with antibiotics. This is consistent with the current approach taken in Canada for animal testing of therapeutic antibiotics. Therefore, the weight of evidence suggest that abortions observed in the rabbit developmental toxicity studies for kasugamycin were likely secondary to severe maternal toxicity as a result of alteration of the intestinal flora, a situation that is considered unique to the rabbit. As a result, the abortions in the rabbit developmental toxicity study are not considered relevant for the evaluation of a potential hazard to the human population.

There was no evidence of neurotoxicity in oral acute and subchronic neurotoxicity studies conducted in rats, nor was there any indication of neurotoxic potential for kasugamycin in the rest of the database.

Although decreases in the number of spleen cells and splenic IgM activity were noted at the highest dose tested in an immunotoxicity study in the mouse, these effects occurred along with mortality, body weight losses and clinical signs of toxicity. There was no effect on immunological parameters at lower doses. In light of this, these findings were attributed to overt systemic toxicity and stress in high-dose animals and were not considered to be an indication of selective immunotoxicity.

Results of the toxicology studies conducted on laboratory animals with kasugamycin and its associated end-use products, are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched and reviewed for kasugamycin. As of April 17, 2012, no incident reports involving kasugamycin for pesticidal use have been submitted to the PMRA.

3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for kasugamycin. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats. There was no trigger for the requirement of a developmental neurotoxicity study.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. Minor developmental effects (increased incidence of shortening and/or absence of the 13th ribs) were observed in the rat developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity characterized by body weight effects, along with an increased incidence of loose stool and distention of the large intestine with stool in the cecum. Abortions preceded by severely decreased food consumption and body weight loss were noted in range-finding developmental toxicity studies in the rabbit; however, no dose-related increase in incidence of abortion was noted in the main study. Effects

noted in these animals prior to abortion were indicative of enterocolitis. As the rabbit has been noted to be highly susceptible to the effects of antibiotics on their gut flora, the abortions observed in the rabbit developmental toxicity studies were considered secondary to severe maternal toxicity as a result of alteration of the intestinal flora and are unique to the rabbit. As a result, the abortions were not considered to be relevant for the evaluation of a potential hazard to the human population.

Overall, endpoints in the young were well-characterized and not considered serious in nature. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

An ARfD for kasugamycin was not determined because an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.

3.3 Acceptable Daily Intake (ADI)

To estimate risk of repeat dietary exposure, the 2-year chronic dietary study in the rat with a no observed adverse effect level (NOAEL) of 11 mg/kg bw/day was selected for risk assessment. At the LOAEL of 116 mg/kg bw/day, testicular effects (softening and atrophy) and renal effects (increased relative weights and brown pigment deposition in the proximal tubular cells) were observed along with increased cecal weights and foam cell aggregation in the lungs. This study provides the lowest NOAEL in the database and incorporates findings from the two target organs. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{11 \text{ mg/kg bw/day}}{100} = 0.1 \text{ mg/kg bw/day of kasugamycin}$$

Cancer Assessment
There was no evidence of carcinogenicity and therefore, no cancer risk assessment is necessary.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposures to Kasumin 2L Bactericide are characterized as short- to intermediate-term for mixers/loaders and applicators, involved in treating the field and greenhouse fruiting vegetables and orchard crops, are predominantly by the dermal and inhalation routes. Postapplication worker exposures for field vegetables and orchards are considered to be short- to intermediate-term duration, but postapplication exposure of workers in greenhouses is considered to be long-term.

Short- and Intermediate-term Dermal
For short- and intermediate-term occupational dermal risk assessment, a NOAEL of 50 mg/kg bw/day from the 21-day dermal toxicity study in rats was selected. At the LOAEL of 100 mg/kg bw/day, decreased thymus weights were observed in females, along with dermal irritation (redness, swelling, scabbing and scarring). This study was selected as it encompasses the relevant route of exposure and assessed the target organs of toxicity. In addition, there was no indication of an increase in toxicity to target organs from short- to intermediate-term dosing.

The target Margin of Exposure (MOE) is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This MOE is considered to be protective of all individuals including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation
A short-term inhalation study was not available. For short- and intermediate-term occupational inhalation risk assessment, a NOAEL of 18 mg/kg bw/day from the 90-day dietary study in rats was selected. At the LOAEL of 58 mg/kg bw/day, renal effects (eosinophilic bodies in proximal tubular cells), increased cecal weights and red blood cell effects were observed. This study was selected as it encompasses the appropriate duration and assessed the relevant target organs of toxicity.

The target MOE is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This MOE is considered to be protective of all individuals including nursing infants and the unborn children of exposed female workers.

Long-term Dermal and Inhalation
For long-term occupational dermal risk assessment, a NOAEL of 11 mg/kg bw/day was selected from the 2-year chronic dietary study in the rat. At the LOAEL of 116 mg/kg bw/day, testicular effects (softening and atrophy) and renal effects (increased relative weights and brown pigment deposition in the proximal tubular cells) along with increased cecal weights and foam cell aggregation in the lungs were observed. No long-term dermal or inhalation studies were available; therefore, this study was selected as it encompasses the appropriate duration and assessed the relevant target organs of toxicity.

The target MOE is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This MOE is considered to be protective of all individuals including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

The short- to intermediate-term dermal endpoint is based on a dermal toxicological study; therefore, no dermal absorption value is needed. The endpoint for long-term dermal exposure is based on an oral toxicological study. Since no dermal absorption study was submitted, the systemic absorption for long-term dermal exposure is assumed to be 100%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator (M/L/A) Exposure and Risk Assessment

Individuals have potential for exposure to Kasumin 2L Bactericide during mixing, loading and application. Dermal and inhalation exposure estimates for workers were generated from the Pesticide Handlers Exposure Database (PHED) version 1.1. The PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. To estimate exposure for each use scenario, appropriate subsets of A and B grade data were created from the database files of PHED for all liquids open mix/loading coupled with application equipment of groundboom, airblast, manually- and mechanically-pressurized equipment, and backpack sprayers. The maximum application rate is 102 grams of active ingredient per hectare for orchard crops, and 24.5 grams of active ingredient per hectare for fruiting vegetables.

Exposure to workers mixing, loading and applying Kasumin 2L Bactericide is expected to be short- to intermediate-term duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders/applicators applying Kasumin 2L Bactericide to orchard crops using airblast equipment, field vegetable crops using groundboom equipment, and greenhouse vegetable crops using manually- and mechanically-pressurized equipment and backpack sprayers. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants, and chemical-resistant gloves.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Dermal exposure was estimated by coupling the unit-exposure values with the amount of product handled per day. A dermal absorption value is not required. Inhalation exposure was estimated by coupling the unit-exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg as an adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL) to obtain the margin of exposure (MOE). The target MOE is 100. Since dermal and inhalation endpoints are not derived from the same toxic effect, dermal and inhalation exposures cannot be combined.

Table 3.4.2.1.1 Mixer/Loader/Applicator Exposure Estimates and Margins of Exposure

Crop	Scenario [1]	Clothing Scenario[1]	ATPD[2] (ha/day)	Total Dermal Exposure[3] M/L/A (mg a.i./kg bw/day)	Dermal MOE[4]	Total Inhalation Exposure[3] M/L/A (mg a.i./kg bw/day)	Inhalation MOE[4]
Orchard pome fruit and walnuts, Farmer or custom	Liquid, open-pour mixing and loading; open-cab airblast	long-sleeved shirt, long pants, and chemical-resistant gloves; for all mixing, loading, and application	20	1.79E-02	2799	2.11E-04	81100
Field-grown, fruiting vegetables, farmer or custom	Liquid, open-pour mixing and loading; groundboom, open cab		26	7.61E-04	65700	2.33E-05	751000
Greenhouse, fruiting vegetables, farmer or custom applicator	Liquid, open pour, manually pressurized sprayer, M/L/A		0.625	2.06E-04	242292	9.89E-06	1770000
	Liquid, open pour, backpack sprayer, M/L/A		0.625	1.19E-03	41972	1.36E-05	1288000
	Liquid, open pour, mechanically-pressurized sprayer, mixer/loader/applicator (also covers automated equipment)		2.3	4.5E-03	11120	1.22E-04	144000

1. Mixer/Loader/Applicator (M/L/A) scenarios based on Pesticide Handlers' Exposure Database (PHED, version 1.1)
2. Default Area-treated-per-day values; hand-held equipment area treated based on default volume sprayed per day
3. Exposure = (Application rate × Area Treated per Day × Unit-Exposure × Dermal Absorption) / (body weight × CF)
   Where, Exposure Time = 8h/day; Dermal absorption = 100% (1.0); CF = conversion 1 mg/1000µg
4. MOE = Exposure / NOAEL; where NOAEL = 50 mg/kg bw/day for dermal exposures; NOAEL = 17.5 mg/kg bw/day for inhalation exposures; target MOE = 100; values rounded to 3 significant digits

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Kasumin 2L Bactericide from hand harvesting, thinning, tying, pinching, pruning, and training. Given the nature of activities performed, dermal contact with treated surfaces is expected. Postapplication inhalation exposure is not expected to be a concern for field activities, as the active ingredient has a low vapour pressure, and the outdoor dilution effect. In addition, postapplication inhalation exposure in greenhouses is not considered to be a concern based on the lower inhalation exposure compared to the dermal exposure (acceptable MOE), and the lower postapplication exposure compared with that of the M/L/A. While the use of greenhouse ventilation systems also reduces airborne residues, the standard restricted entry interval of 12 hours further ensures that the foliar residues have dried. The duration of exposure is considered to be short- to intermediate-term for field workers and long-term for greenhouse workers. The primary route of exposure for workers re-entering treated areas would be through the dermal route.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer co-efficients. Activity-specific transfer co-efficients are based on data collected by the Agricultural Re-entry Task Force (ARTF). Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate and daily dissipation of 10% for field crops, or 0% dissipation for greenhouses are used to assess exposures.

Exposure estimates were compared to the toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 100.

Table 3.4.2.2.1 Postapplication Exposure Estimates and Margins of Exposure for Re-entry into Treated Areas

Tasks[1]	Application rate (µg/cm^2)	Number of Applications	Application Interval (days)	DALA (days)	DFR[2] (µg/cm^2)	Transfer Coefficients[1] (cm^2/h)	Exposure[3] (mg/kg bw/day)	MOE[4]
Field crops								
pome fruit (thinning)	1.02	4	7	0	0.3706	3000	0.127050	394
walnut trees (mechanically harvest nuts)	1.02	4	14	100	7.01E-06	200	1.60E-07	3.12E+08
fruiting vegetables (hand line irrigation)	0.245	3	7	0	0.0836	1100	0.0105	4755
Greenhouse crops								
All activities for greenhouse crops	0.245	3	7	0	0.1470	1800	0.0302	364

Note: DALA is 'Days After Last Application'

1. Tasks and transfer co-efficients representative of highest exposure postapplication tasks for label crops (Agricultural Re-Entry Task Force database)
2. Dislodgeable foliar residues (DFR) based on dislodgeable residue on the day of application (default 20%); daily dissipation (10% in fields; 0% in greenhouses); re-entry on days after last application
3. Exposure = (DFR × Transfer Co-efficient × Exposure Time × Dermal Absorption) / (body weight × CF)
   Where, Exposure Time = 8 h/day; Dermal absorption value not required for short- to intermediate endpoint, and considered to be 100% (1.0) for the long-term endpoint; CF = conversion 1mg/1000µg
4. MOE = Exposure / NOAEL; NOAEL = 50 mg/kg bw/day for field crops; 11 mg/kg bw/day for greenhouse crops; target MOE = 100

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

There are no domestic class products; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

Applications can be made to pome fruit crops (apples, pears) in pick-your-own (PYO) orchards, where patrons (includes adults, youth and children) enter the treated orchards to pick fruit for personal uses and consume the fruit on the same day. Acute endpoints appropriate for a PYO aggregate scenario were not selected. Also, since the pre-harvest interval (PHI) is 90 days after the last application, dislodgeable foliar residues are expected to be very low and pose no exposure concerns.

There is potential for exposure to adults and youth contacting residential fruit trees that have been commercially treated with Kasumin 2L Bactericide, through contact with transferable residues. Children are not expected to engage in activities associated with the treated trees (for example, pruning). Short- to intermediate-term exposure is expected as the use pattern allows up to four applications. Postapplication inhalation exposure is not expected to be a concern as the active ingredient has a low vapour pressure and there is an outdoor dilution effect. Dermal exposure is estimated by coupling dislodgeable foliar residue values with activity-specific transfer co-efficients. Activity specific transfer co-efficients are based on data collected by the Agricultural Re-entry Task Force (ARTF), and scaled from adult to youth. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate and daily dissipation of 10% are used to assess exposures.

Exposure estimates, when compared to the toxicological endpoint, resulted in margins of exposure that exceeded the target MOE of 100.

Table 3.4.3.2.1 Postapplication Exposure and Risk Estimates for Residential Contact with Treated Trees

Sub-Population (age range, years-old)	Dislodgeable foliar residue (0 days after 4th application) (µg/cm²)	Transfer co-efficient[1] (cm²/h)	Dermal Exposure[2] (mg/kg bw/day)	MOE[3] (target = 100)
Adults (19-75)	0.3706	1500	0.00532	9398
Youth (10-18)		1034	0.00658	7596

1. Only adults and youths are expected to contact transferable residues represented by hand harvesting
2. Dermal Exposure = (DFR × Transfer Co-efficient × Exposure Time × Dermal Absorption) / (body weight × CF)
   Where, Exposure Time = 0.67 h/day; Dermal absorption = 100% (1.0); CF = conversion factor 1mg/1000µg
3. MOE = NOAEL/Exposure; NOAEL of 50 mg/kg bw/day, from the rat 21-day dermal study, was determined to be most appropriate for short- to intermediate-term dermal exposures. The target MOE is 100.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Applications will be made only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal (ruminant) commodities is kasugamycin. The data gathering/enforcement analytical methods are valid for the quantitation of kasugamycin residues in tomato, pepper, apple, pear and walnut matrices. The residues of kasugamycin are stable when stored in a freezer between -40°C and -0.2°C for 714 days (pepper), 1003 days (tomato), 705 days (tomato paste), 693 days (tomato puree), 308 days (apple), 197 days (apple juice), 204 days (wet apple pomace), 233 days (pear) and 859 days (walnut nutmeat). Raw agricultural commodities of tomato and apple were processed in tomato puree and paste and apple juice and pomace. Residues of kasugamycin were only found to concentrate in apple juice with a processing factor of 1.25. Supervised residue trials conducted throughout the United States and Canada using an end-use product containing kasugamycin at proposed rates in or on pepper, tomato, apple, pear and walnut are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

A basic chronic risk assessment was conducted using the following assumptions: 100% crop treated, proposed MRLs, default processing factors and general MRL of 0.1 ppm for cattle matrices including milk. The basic chronic dietary exposure from all supported kasugamycin food uses (alone) for the total population, including infants and children, and all representative population subgroups are 0.6% of the acceptable daily intake (ADI). Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to kasugamycin from food and water is 0.6% (0.000643 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 3.0% (0.002996 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified. Thus, no acute dietary exposure assessment was conducted.

3.5.3 Aggregate Exposure and Risk

Pick-Your-Own scenarios were considered for apple and pear crops. However, as there was no acute toxicological endpoint(s) identified for children, or the general population, a quantitative risk assessment was not required.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Fruiting vegetables (CG 8-09)	0.1
Pome fruits (CG 11-09)	0.2
Walnuts	0.04

For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 4 and 5.

3.6 Antimicrobial Resistance Assessment

The potential for adverse human and animal health effects resulting from the transfer of kasugamycin resistance to human and animal pathogens was assessed by the PMRA and determined to be low (i.e. not a concern). Kasugamycin has a narrow spectrum of bactericidal activity and is not effective against common human or animal pathogens at practical use level. As a result, kasugamycin has not been used as a human or as an animal antibiotic, and is unlikely to be used in the future. If resistance were to develop in target pests, it is not expected to be of concern because the target site of protein synthesis for kasugamyccin is different from the target sites of other aminoglycoside antibiotics. Also, there are no reports of cross resistance or co-resistance to other aminoglygcosides in published scientific literature.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate data for kasugamycin are summarized in Appendix I, Table 6.

Kasugamycin is very soluble in water and has a low potential to bioaccumulate. The vapour pressure and Henry's Law Constant indicate it is relatively non-volatile under field conditions. Kasugamycin is expected to dissociate at environmentally relevant pHs. Physical/chemical properties of kasugamycin are summarized in Section 1.2. No physical/chemical properties were provided for the major transformation products, kasugamycinic acid or kasuganobiosamine.

Based on their chemical structures, however, they are expected to be more soluble than the parent and less likely to bioaccumulate.

In soil, hydrolysis increases with increasing pH (half-lives of 77.9 days at pH 7, and 11.4 days at pH 9) and temperature, and may be an important transformation process of kasugamycin in the environment, with kasugamycinic acid being the major transformation product produced. Phototransformation of kasugamycin on soil is not expected to be an important route of transformation. Kasugamycin undergoes biotransformation and is moderately persistent in aerobic soil with CO_2 as the only major transformation product. When oxygen levels are low, kasugamycin may be more persistent.

Mobility of kasugamycin was assessed. Kasugamycin has low sorption potential in soils (K_{oc}/K_{Foc} = 6.4 to 316). This molecule contains both acidic and basic functional groups which are expected to dissociate at environmentally relevant pHs. However, it could not be predicted if kasugamycin would be negatively or positively charged in soil and how this might impact soil mobility. An assessment of leaching potential was based on laboratory studies of mobility (adsorption, soil/column leaching), the GUS classification scheme (PMRA# 1918524), criteria of Cohen et al. (PMRA# 1918520), groundwater modelling data, and terrestrial field dissipation studies (four soils). While some data suggest that kasugamycin would be a borderline leacher, this conclusion was not supported by the field dissipation study or groundwater modelling results. In the soil/column leaching study, the transformation product, kasugamycinic acid, had greater leaching potential than the parent, but the field dissipation study results only detected it in the upper layers of the soil profile. Overall, kasugamycin and its transformation products are not expected to leach and are unlikely to persist in the terrestrial environment.

In water, biotransformation is expected to be an important route of transformation of kasugamycin. Photolysis in water is unlikely to be important whereas hydrolysis, particularly at basic pH, may contribute to the transformation of kasugamycin. In aerobic water/sediment systems (pH ranging 7.8 to 8.1), kasugamycin is slightly persistent based on half-lives in the whole system. Kasugamycin readily partitions to sediment where it transforms more slowly. Kasugamycinic acid (KSMA) is a major transformation product and it remains primarily in the water where it appears to be moderately persistent. The other major transformation product is CO_2. Under anaerobic conditions in a water/soil system, kasugamycin is moderately persistent and was detected in both water and soil phases, with more residues being distributed in the soil initially (first 14 days of the study period). Kasugamycinic acid appeared as a major transformation product after approximately 4 months in the laboratory study and remained primarily in the water. Kasuganobiosamine was also found as a major transformation product under anaerobic aquatic conditions (after 6 months into the study period) and was found in both water and soil compartments. Overall, both major transformation products decreased in concentration by the end of the 368-day period.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Screening level EECs for kasugamycin in soil, water, and on plant surfaces are in Appendix I, Table 7. Appendix I, Table 8 lists the estimated concentrations in food sources for birds and mammals.

4.2.1 Risks to Terrestrial Organisms

A risk assessment was undertaken for terrestrial organisms as there is a potential for direct or indirect exposure to kasugamycin through a spray application. Screening level EECs were based on four cumulative applications of 102 g a.i./ha (7-day intervals). For cases where the LOC is exceeded, (i.e. RQ $\geq$ 1), a refined assessment is conducted. The information available for kasugamycin was sufficient to characterize the potential risks. A summary of the terrestrial toxicity data is presented in Appendix I, Table 9. The calculated risk quotients are summarized in Appendix I, Tables 10 and 11 (screening level), and Table 12 (refined – spray drift only).

Earthworms: Kasugamycin was not acutely toxic to earthworms. The LOC was not exceeded (RQ < 0.0003) indicating that kasugamycin is not expected to pose a risk to earthworms.

Honeybees (pollinators): Acute oral and contact exposure to kasugamycin did not result in significant mortality or sub-lethal effects in honey bees. The LOC was not exceeded for either acute contact or acute oral exposure studies ($RQ_{contact} < 0.002$ and $RQ_{oral} = 0.0067$) indicating that kasugamycin is not expected to pose a risk to honeybees or other pollinators.

Birds: Acute oral exposure to kasugamycin had negligible toxicity to bobwhite quail (*Coturnix virginianus*), mallard (*Anas platyrhynchus*) and zebra finch (*Taeniopygia guttata*), with no treatment-related mortalities or clinical effects occurring in any species. In reproductive toxicity studies conducted with bobwhite quail and mallard, no treatment-related adverse effects on reproductive parameters or on the parental generations were observed up to 1000 mg a.i./kg diet, the highest concentration tested. The screening level risk assessment was based on three size classes of birds and conservative estimates of pesticide residues in food sources. No LOCs were exceeded (all RQ values were ≤ 0.13) indicating that kasugamycin is not expected to pose an acute or reproductive risk to birds.

Mammals: Kasugamycin was not acutely toxic to rats. For chronic effects, the two generation rat reproduction study showed evidence of a treatment-related effect on reproduction or development, with a reduction in fertility and fecundity in the F_1 parents for both litters and increased pre-coital interval during the mating period for the F_2 litter. Thus, the NOAEL was determined to be 70.3 mg a.i./kg bw/day for males and 82.9 mg a.i./kg bw/day for females. The screening level risk assessment was based on three size classes of mammals and conservative estimates of pesticide residues in food sources. No LOCs were exceeded (all RQ values were ≤ 0.29) indicating that kasugamycin is not expected to pose an acute or reproductive risk to small mammals.

Non-target plants: The toxicity of the end-use product Kasumin 2L Bactericide (2.18% free base) to non-target plants was determined in vegetative vigour and seedling emergence assays using standard crop species.

For the study of vegetative vigour, no statistically significant treatment-related adverse effects were observed in any plant species in the vegetative vigour assay at the rate the product was tested (98.15 g a.i./ha). The test rate did not, however, account for four cumulative applications over a season of use. A conservative assessment of risk, where an $ER_{25} = 98.15$ g a.i./ha is assumed, results in an RQ of 2.32. Had testing been conducted with higher rates to determine the actual ER_{25}, the RQ would be even lower. Therefore, kasugamycin is not expected to pose a risk to plants through a direct application to foliage.

For the study of seedling emergence, two crop species showed an adverse effect > 25% for shoot dry weight at the rate that was tested (98.15 g a.i./ha; 26% for wheat, 37% for onion). Using a soil-applied EEC of 353.76 g a.i./ha (maximum seasonal application rate) for seedling emergence for onion, the screening level risk assessment identified a potential risk to plants (RQ > 3.60, exceeds the LOC). For a more refined assessment, exposure due to drift from an early-season airblast application, estimated at 74% of the full application rate, was considered

with the endpoint for onion. The LOC was still exceeded (RQ > 2.67). Based on these results, a potential for risk to non-target plants at the proposed Canadian use rate was concluded and a no-spray buffer zone is being recommended.

4.2.2 Risks to Aquatic Organisms

A risk assessment was undertaken for aquatic organisms as there is a potential for exposure through spray drift and surface water run-off. To assess the potential for adverse effects, screening level EECs in the aquatic environment, based on four cumulative applications of 102 g a.i./ha (7-day intervals) to water were calculated for freshwater and marine aquatic organisms. For cases where the LOC is exceeded (i.e. RQ $\geq$ 1), a refined assessment is conducted to determine risk resulting from spray drift and runoff separately. The information available for kasugamycin was sufficient to characterize the potential risks. A summary of aquatic toxicity data for kasugamycin and the end use product Kasumin 2L Bactericide is presented in Appendix I, Table 13. The calculated risk quotients are summarized in Appendix I, Table 14.

Freshwater invertebrates: Acute and chronic exposure of *Daphnia* to kasugamycin did not result in any adverse effects. When compared to EECs, the LOC was not exceeded (RQ values $\leq$ 0.0014). Kasugamycin is not expected to pose a risk to freshwater invertebrates.

Freshwater fish: The acute risk of kasugamycin to fish was assessed for two species (rainbow trout and fathead minnow) and for chronic exposure, one species was tested (fathead minnow). At the screening level assessment, the risk of kasugamycin to fish was negligible (RQ values $\leq$ 0.0047) and the LOC was not exceeded for either acute or chronic exposure. Kasugamycin is not expected to pose a risk to freshwater fish.

Amphibians: The screening level risk assessment was conducted by comparing EECs in a 15 cm water depth with fish toxicity endpoints as surrogates for aquatic life-stages of amphibians. The LOC was not exceeded and kasugamycin is not expected to pose a risk to amphibians.

Freshwater algae and plants: The acute risk of kasugamycin to freshwater algae and plants was assessed for three algal and one vascular plant species. Screening level RQs were all $\leq$ 0.1184, indicating that kasugamycin is not expected to pose a risk to these organisms.

Marine species: Kasugamycin posed negligible acute risk to the saltwater diatom (*Skeletonema costatum*), Eastern oyster (*Crassostrea virginica*), mysid (*Americamysis bahia*), and sheepshead minnow (*Cyprinidon variegates*) where all the screening level RQ values were $\leq$ 0.0041.

4.2.3 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched for kasugamycin. As of May 15, 2012, there were no health-related incident reports for this active in the PMRA Incident Reporting database.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Suppression of bacterial spot on greenhouse and field fruiting vegetables

Kasumin 2L Bactericide was tested against bacterial spot on field tomatoes (2 trials), field peppers (3 trials) and greenhouse peppers (5 trials). Field trials were conducted in Manitoba and Ontario. The bactericide was usually applied three times at 0.6 and 1.2 L/ha and compared to the commercial standard Kocide 2000.

Kasumin 2L Bactericide and Kocide 2000 provided significant reductions of disease incidence and severity when compared to the untreated control, but did not consistently control bacterial spot under various disease pressures. Adequate control is difficult to achieve through the use of copper when weather conditions are optimal for disease development. Kasumin 2L Bactericide performed similarly in the greenhouse and in the field. The weight of evidence supports the use of Kasumin 2L Bactericide for suppression, instead of control, of bacterial spot on greenhouse and field fruiting vegetables.

5.1.1.2 Suppression of bacterial stem canker on greenhouse and field fruiting vegetables

Two field trials from Ontario and Manitoba and four greenhouse trials on tomatoes were provided in support of the proposed claim. The suppressive effect of Kasumin 2L Bactericide at 1.2 L/ha on the incidence of bacterial stem canker was shown in one field study. Disease severity, although at low levels, was adequately controlled in the same trial. Significant but low disease reduction was achieved with Kasumin 2L Bactericide in the remaining field and greenhouse trials. However, despite the severe disease pressure noted in these trials, Kasumin 2L Bactericide resulted in notable yield increases that averaged 128% of the untreated control. Moreover, Kasumin 2L Bactericide provided at least comparable levels of protection as the commercial standards. In light of the above efficacy and yield considerations, the use of Kasumin 2L Bactericide is supported for suppression, instead of control, of bacterial stem canker on field and greenhouse tomatoes.

5.1.1.3 Tank-mixes of Kasumin 2L Bactericide with Kocide fungicides

Tank-mixes of Kasumin 2L Bactericide with Kocide DF, Kocide 101 or Kocide 2000, which contain copper hydroxide, were proposed for broad disease control on greenhouse and field fruiting vegetables. The purpose of the tank-mixes is to reduce the risk of resistance development in bacterial populations. Kasumin 2L Bactericide at 5.0 L/ha was tank-mixed with Kocide 2000 in several trials on walnut blight, resulting in adequate disease control without any adverse effects. Based on resistance management considerations, the tank-mix of Kasumin 2L Bactericide with Kocide DF, Kocide 101 or Kocide 2000 is supported for control of the registered bacterial diseases on tomatoes and peppers (greenhouse seedlings for transplant, field). The most restrictive label limitations and precautions must be followed.

5.1.1.4 Control of fire blight on pome fruits

A total of 19 efficacy trials tested Kasumin 2L Bactericide against fire blight on 5-47 year-old pear (4) and apple (15) trees. Trials included varieties grown on M9, M26 and M29 rootstocks, and with different susceptibilities to fire blight. U.S. trials from non-neighbouring states were considered acceptable for review given that fire blight epidemics are triggered by very specific environmental conditions that occur in all listed locations, i.e. warm and humid weather during bloom. Seven apple trials were not reviewed, as the tested rates exceeded the proposed rates by 40-180%.

Ten out of 12 trials on apples and pears showed that Kasumin 2L Bactericide at 5.0 L/ha provided adequate fire blight control (7 trials) or was at least statistically comparable to the commercial standard streptomycin (3 trials), even if the latter was often applied at rates higher than what is commonly applied in Canadian orchards. For these reasons, the use of Kasumin 2L Bactericide is supported for control of fire blight on pome fruits.

5.1.1.5 Suppression of walnut blight on walnuts

A total of 17 field trials were carried out in California from 2006-2010. Trials were conducted in Fresno, Solano and Yuba-Sutter in the months of May and June, whose average monthly temperatures were found to be relatively similar to that of certain Canadian growing regions such as British Columbia. Furthermore, walnut blight development is highly dependent on the environmental conditions in the spring, i.e. high rainfall, cool and wet weather. Therefore, the disease pressure conditions noted in the field studies could very well have occurred in Canada. For the above reasons, the California trials are considered acceptable for review.

In most trials, Kasumin 2L Bactericide applied four to seven times at 5.0 L/ha suppressed walnut blight and provided lower efficacy than copper-mancozeb tank-mixes, which are considered as the reference treatments for walnut blight control in the U.S. The use of Kasumin 2L Bactericide is supported for suppression, instead of control, of walnut blight on walnut.

5.2 Economics

No market analysis was performed for this application.

5.3 Sustainability

5.3.1 Survey of Alternatives

Refer to Appendix I, Table 16 for a summary of the active ingredients currently registered for the uses supported with Kasumin 2L Bactericide.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Kasumin 2L Bactericide has shown to be compatible in tank-mix with fixed copper products commonly used for management of bacterial diseases on the proposed crops. Kasumin 2L Bactericide is for use as part of an integrated pest management program.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

A review of scientific literature was conducted to evaluate the risk of cross-resistance between kasugamycin and streptomycin. Cross-resistance is said to occur when resistance to one active ingredient in a pathogen population confers resistance to another active ingredient. Although the two bactericides both inhibit protein synthesis by preventing the incorporation of amino acids into proteins, the ribosome sites involved are close but distinct.

Evidence from scientific literature showed that kasugamycin-resistant mutants of *Escherichia coli*, *Bacillus subtilis* and *Pyricularia oryzae* have been produced in vitro without any reports of cross-resistance to streptomycin. Low correlation coefficients were found between sensitivity to kasugamycin and streptomycin in *E. amylovora* isolates from California pear orchards, thus indicating that cross-resistance was not observed in the sample population. There is no indication of cross-resistance between kasugamycin and streptomycin based on their distinct sites of activity and the reviewed evidence.

Kasugamycin is classified under Group 24 (hexopyranosyl antibiotics) by the Fungicide Resistance Action Committee (FRAC) and the risk of resistance development in plant pathogens has been evaluated as medium. Kasugamycin-resistant populations of *P. oryzae*, the causal agent of rice blast, had become a serious problem in Japanese rice fields in the 1970s where kasugamycin was in continuous use. The applicant associated these cases of resistance with an overuse of the product. The pathogenic bacteria targeted by Kasumin 2L Bactericide have been shown to develop resistance to streptomycin and a risk of resistance development to kasugamycin exists. Resistance development in pathogenic bacteria could occur through the selection of spontaneous mutants or the acquisition of a kasugamycin resistance gene by horizontal DNA transfer.

Adequate measures have been implemented by the applicant to mitigate the risk of plant pathogen resistance development to kasugamycin: 1) a maximum of three (fruiting vegetables) or four (pome fruits, walnut) kasugamycin applications per season, 2) a maximum of two sequential applications of Kasumin 2L Bactericide before alternating with a different mode of action bactericide, and 3) prohibition of certain cultural practices such as alternate row spraying in pome fruits.

5.3.4 Contribution to Risk Reduction and Sustainability

Few pest control products are available for the management of bacterial diseases on fruiting vegetables (bacterial spot, bacterial stem canker), pome fruits (fire blight) and walnut (walnut blight). Kasumin 2L Bactericide represents a valuable disease management tool and a suitable rotational partner to commonly used bactericides. Its integration into spray programs may reduce the reliance on fixed copper products and streptomycin. Copper- and streptomycin-resistant bacterial strains have been widely reported, resulting in reduced product efficacy. Copper also cannot be applied during hot summer days, as it poses risks of phytotoxicity.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, kasugamycin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Kasugamycin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 15 for comparison with Track 1 criteria.
- Kasugamycin is a naturally-occurring substance. It is not expected to be persistent or bioaccumulative (log K_{ow} < -1.96; pH 5) in the environment.
- Kasugamycin does not form any transformation products that meet all Track 1 criteria. The major transformation products, kasugamycinic acid and kasuganobiosamine, are expected to be more soluble than the parent compound and less likely to bioaccumulate.

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade kasugamycin and the end-use product Kasumin 2L Bactericide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for kasugamycin is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Kasugamycin was not neurotoxic or immunotoxic. In short-term and chronic studies on laboratory animals, the primary targets were the kidneys and testes. The risk assessment protects against these toxic effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

The nature of the residue in rice, lettuce and tomato plants and lactating goat is adequately understood. The residue definition in livestock (ruminants), plants and rotational crops, for enforcement and risk assessment purposes, is kasugamycin. The proposed use of kasugamycin on fruiting vegetables (CG 8-09), pome fruits (CG 11-09) and walnuts does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend that the following maximum residue limits be specified for residues of kasugamycin:

- 0.1 ppm in and on fruiting vegetables (CG 8-09)
- 0.2 ppm in and on pome fruits (CG 11-09)
- 0.04 ppm in and on walnuts

Mixers, loaders, and applicators handling Kasumin 2L Bactericide, and workers re-entering treated orchards and field and greenhouse fruiting vegetables, are not expected to be exposed to levels of Kasumin 2L Bactericide that will result in an unacceptable risk when the Kasumin 2L Bactericide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Postapplication residential exposure to individuals contacting treated fruit trees is not expected to result in unacceptable risk when Kasumin 2L Bactericide is used according to label directions. Health risks for people who enter treated Pick-Your-Own orchards are not a concern.

Health risks to bystanders are not a concern.

7.2 Environmental Risk

Kasugamycin is moderately persistent in soil and water, and is not expected to volatilize from moist soils or water surfaces. Transformation products are not of environmental concern. Leaching to groundwater of kasugamycin and its transformation products is not expected to be of concern.

Kasugamycin, and its end-use product Kasumin 2L Bactericide is not expected to pose a risk to non-target aquatic and terrestrial organisms at the proposed Canadian use rates, except for terrestrial vascular plants. A no-spray buffer zone of 2 metres is, therefore, proposed to mitigate the risk from spray drift to terrestrial habitats.

7.3 Value

The data submitted to register Kasumin 2L Bactericide are adequate to support the following claims:

- suppression of bacterial spot on greenhouse and field fruiting vegetables
- suppression of bacterial stem canker on greenhouse and field fruiting vegetables
- control of fire blight on pome fruits
- suppression of walnut blight on walnut

Kasumin 2L Bactericide is considered a high priority in the Canadian Grower Priority Database for control of fire blight on apples and pears as well as a low priority for control of bacterial diseases on tomatoes and peppers (greenhouse and field).

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Kasugamycin Technical Bactericide and Kasumin 2L Bactericide, containing the technical grade active ingredient kasugamycin, to control or suppress bacterial diseases on greenhouse and field fruiting vegetables, pome fruits and walnuts.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	female
µg	micrograms
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ALK	alkaline phosphatase
ARfD	acute reference dose
ARTF	Agricultural Re-Entry Task Force
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
BAF	bioaccumulation factor
BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CF	conversion factor
CG	crop group
CK	creatine kinase
cm	centimetres
d	days(s)
DALA	days after last treatment
DAT	day(s) after treatment
DFOP	double first-order in parallel
DFR	dislodgeable foliar residues
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
E_rC_{50}	EC_{50} in terms of reduction of growth rate
E_yC_{50}	EC_{50} in terms of reduction of yield
EDE	estimated daily exposure
EEC	estimated environmental concentration
EMEA	European Medical Agency
EP	end-use product
ER_{25}	effective rate for 25% of the population
F_1	first generation

F_2	second generation
fc	food consumption
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
fw	fresh weight
g	gram
GAP	good agricultural practices
GD	gestation day
GI	gastrointestinal
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HPLC	high performance liquid chromatography
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{Foc}	Freundlich organic-carbon partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KSMA	Kasugamycinic acid
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LLMV	lowest limit of method validation
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LSC	liquid scintillation counting
m	metre
mg	milligram
mL	millilitre
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
M/L/A	mixer/loader/applicator
MOE	margin of exposure
mPa	millipascals
MRL	maximum residue limit
MS/MS	tandem mass spectrometry
NA	not applicable
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
OC	organic carbon content

P	parental generation
PBI	plantback interval
PES	post extraction solids
PF	processing factor
pH	potential of hydrogen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PYO	pick-your-own
RAC	raw agricultural commodity
RBC	red blood cells
rel	relative
RQ	risk quotient
RTI	retreatment interval
SD	standard deviation
SFO	single first-order
T_{max}	time to maximum concentrations
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		PMRA #
Soil and sediment	Not stated	Kasugamycin Kasugamycin acid	HPLC-MS/MS	0.01 mg/L		1890012
Water	Not stated	Kasugamycin	HPLC-MS/MS	0.05 mg/L		1889884; 2038045
Plant	Modified #Meth-146 (Revision #4)	Kasugamycin	HPLC-MS/MS	0.04 ppm	Whole pepper, whole tomato, walnut nutmeat	1890008; 1890010-18900011
	#Meth-146 (Revision #4) – enforcement method		HPLC-UV	0.04 ppm	Whole pepper, whole tomato	1890026-1890027
	FEQL Project No. 0407	Kasugamycin	HPLC-UV	0.04 ppm	Whole apple	1890009
	FEQL Project No. 0706	Kasugamycin	HPLC-UV	0.04 ppm	Whole pear	1890007
	Modified #Meth-146 (Revision #4)	Kasugamycin	HPLC-UV	0.04 ppm	Whole pear	2136698

Table 2 Toxicity Profile of Kasumin 2L Bactericide

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Sprague-Dawley rat PMRA # 1890015	LD_{50} (♀) > 5000 mg/kg bw **Low toxicity**
Acute Dermal Toxicity Sprague-Dawley rat PMRA # 1890016	LD_{50} > 2000 mg/kg bw **Low toxicity**
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA # 1890017	LC_{50} > 2.05 mg/L **Low toxicity**

Study Type/Animal/PMRA #	Study Results
Acute Inhalation Toxicity Wistar rat PMRA # 1890028	LC_{50} > 4.892 mg/L **Low toxicity**
Eye Irritation NZW rabbit PMRA # 1890018	MAS = 3.4/110 MIS = 9.4/110 (Observed at 1 hour) **Minimally irritating**
Dermal Irritation NZW rabbit PMRA # 1890019	MAS = 0.1/8 MIS = 0.7/8 (Observed at 1hour) **Minimally irritating**
Dermal Sensitization (Beuhler test) Hartley guinea pig PMRA # 1890020	**Non-sensitizer**

Table 3 Toxicity Profile of Technical Kasugamycin
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Crl:CD BR rat PMRA # 1889905	LD_{50} > 5000 mg/kg bw No mortality, clinical signs of toxicity, effects on body weight, or gross lesions. **Low Toxicity**
Acute Dermal Toxicity NZW rabbit PMRA # 1889960	LD_{50} > 2000 mg/kg bw No mortality, clinical signs of toxicity, effects on body weight, or gross lesions. **Low Toxicity**
Acute Inhalation Toxicity (whole body) Sprague-Dawley rat PMRA # 1889897	LC_{50} > 2.07 mg/L Hunched posture and hypoactivity noted during the exposure period. No mortality, effects on body weight, or gross lesions. **Low Toxicity**

Study Type/Animal/PMRA #	Study Results
Eye Irritation NZW rabbit PMRA # 1889899	MAS = 2.6 MIS = 5.7 (observed at 24 hours) **Minimally Irritating**
Dermal Irritation NZW rabbit PMRA # 1889900	MAS = 3.3 MIS = 5.7 (observed at 1, 24 & 48 hours) **Moderately Irritating**
Dermal Sensitization (Buehler) Hartley albino guinea pig PMRA # 1941268	**Not a skin sensitizer**
90-Day Dietary CD-1 mouse PMRA # 1889906	NOAEL = 135/171 mg/kg bw/day LOAEL = 409/566 mg/kg bw/day Based on mortality, perianal reddening; ↑ neutrophil counts, ↑ tubular dilatation and tubular degeneration in testes, spermatoceles (♂); ↓ cholesterol, red perianal staining and darkening of perianal region (gross necropsy), basophilia/hyperplasia in pars recta of kidney (♀).
90-Day Dietary Wistar rat PMRA # 1889908	NOAEL = 18/20 mg/kg bw/day LOAEL = 58/69 mg/kg bw/day Based on ↓ hematocrit, ↓ hemoglobin, ↓ erythrocyte, ↑ cecum wt, ↑ cosinophilic bodies in proximal tubular cells of the kidneys (♂); ↑ foam cell aggregation in the lung (♀).
90-day Dietary Beagle dog PMRA # 1889920	NOAEL = 11 mg/kg bw/day LOAEL = 106/108 mg/kg bw/day Based on ↓ urinary pH, swollen mouth, thickened skin at the commissure of the mouth, tongue lesions (atrophy of dorsal epithelium, serous exudate, loss of epithelial papillae of the dorsal surface, chronic active inflammation, ulceration), excessive salivation, ↓ bwg, ↓ ALK, ↓ urinary volume, ↑ urinary specific gravity (♂); ↓ cholesterol, ↓ CK, ↑ ovary wt, ↑ rel. kidney wt (♀).
12-Month Dietary Beagle dog PMRA # 1889926	NOAEL = 100/104 mg/kg bw/day LOAEL was not established.
Range-finding 7-Day Dermal Sprague Dawley rat PMRA # 1889939	A NOAEL was not established as this was a dose range-finding study. Adverse effects at 250 mg/kg bw/day included pinpoint scabbing and erythema (♀ only). At 500 mg/kg bw/day, erythema was noted (♂) and edema, ↓ bwg and ↑ monocyte counts were observed (♀).

Study Type/Animal/PMRA #	Study Results
21-Day Dermal Sprague Dawley rat PMRA # 1889940	NOAEL (dermal) = 50 mg/kg bw/day (♂ and ♀) LOAEL (dermal) = 100 mg/kg bw/day (♀) Based on scabbing and reddening of skin, erythema, edema, pinpoint scabbing, brown discoloration, scarring, minimal acanthosis and minimal acute inflammation of the skin. LOAEL (dermal) = 250 mg/kg bw/day (♂) Based on scabbing and reddening of skin, erythema. NOAEL (systemic) = 50 mg/kg bw/day (♂ and ♀) LOAEL (systemic) = 100 mg/kg bw/day (♀) Based on ↓ thymus wt. Renal tubular regeneration and kidney mineralization were noted at the next highest dose level. LOAEL (systemic) = 250 mg/kg bw/day (♂) Based on ↓ spleen wt. Renal tubular regeneration was noted at the next highest dose level.
78-Week Dietary CD-1 mouse PMRA # 1889930	NOAEL (♂) = 35 mg/kg bw/day NOAEL (♀) = 215 mg/kg bw/day LOAEL (♂) = 186 mg/kg bw/day Based on ↓ bwg, ↓ fe, ↓ spleen wt. LOAEL was not established for ♀. No evidence of oncogenicity
2-Year Dietary Wistar rat PMRA # 1889914	NOAEL = 11/13 mg/kg bw/day LOAEL = 116/140 mg/kg bw/day Based on ↓ ALK, ↓ creatinine, ↑ cecum wt, ↑ rel. kidney wt, ↑ brown pigment deposition of proximal tubular cells of the kidneys, ↑ foam cell aggregation in the lungs; ↓ total protein, ↓ globulin, ↑testicular softening and severity of atrophy, ↑ nasal rhinitis (♂), ↓ cholesterol values, ↓ liver wt, ↓ ovary wt, ↑ rel. salivary gland wt, ↑ hepatocelluar atrophy (♀). No evidence of oncogenicity.

Study Type/Animal/PMRA #	Study Results
Multigeneration Reproductive Toxicity Sprague-Dawley rat PMRA # 1889911	Parental Toxicity NOAEL = 14/83 mg/kg bw/day LOAEL (♂) = 70 mg/kg bw/day Based on ↓bw, ↓bwg (P). At the next dose the following effects were noted: red swollen skin around anal opening, rectum lesions included red foci areas, chronic active inflammation, ulceration (P/F_1), thickened walls of the rectum, small testes (9/24), fluid filled testes (16/24) (F_1), squamous cell hyperplasia at the ano-rectal junction(P), unilateral atrophy/degeneration of testes (P), bilateral atrophy/degeneration of testes (marked to severe), pelvic dilatation of kidneys, chronic progressive nephropathy (F_1). LOAEL (♀) = 503 mg/kg bw/day Based on red swollen skin around anal opening, rectum lesions included red foci areas, chronic active inflammation, ulceration (P/F_1). Reproductive Toxicity NOAEL = 70/83 mg/kg bw/day LOAEL = 425/503 mg/kg bw/day Based on ↓fertility index (F_1), ↓fecundity (F_1), ↑ pre-coital interval in the 2nd mating of the F_1 generation (5.73 vs 2.23 days in control). Offspring Toxicity NOAEL = 425/503 mg/kg bw/day LOAEL was not established. No evidence of sensitivity of the young.
Range-finding Developmental Toxicity (gavage) Sprague-Dawley rat PMRA # 1889909	A NOAEL was not established as this was a dose range finding study. Maternal effects noted at 1000 mg/kg bw/day included: ↑ loose stool, slight ↓ bw, ↓ bwg, ↓ adjusted bw and ↓ fc. There were no developmental effects observed at any dose level.
Developmental Toxicity (gavage) Sprague-Dawley rat PMRA # 1889910	Maternal NOAEL = 200 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Based on ↑ loose stool, ↓ bw, ↓ bwg, ↓ fc, ↑ distention of large intestine with stool in cecum. Developmental NOAEL = 200 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Based on ↑ shortening and/or absence of 13th ribs No evidence of sensitivity of the young.

Study Type/Animal/PMRA #	Study Results
Range-finding Developmental Toxicity (gavage) NZW rabbit PMRA # 1889927	A NOAEL was not established as this was a dose range-finding study. Maternal effects at 250 mg/kg bw/day and above included bw loss and ↓ fc. All dams sacrificed GD 14-16 due to severe maternal toxicity. No litters available for assessment of developmental effects.
Range-finding Developmental Toxicity (gavage) NZW rabbit PMRA # 1889927	A NOAEL was not established as this was a dose range-finding study. Maternal effects at 30 mg/kg bw/day included bw loss, ↓ fc and one abortion. At the next dose death (1, GD 21), bw loss, ↓ fc and 3 abortions were noted. Developmental effects at 30 mg/kg bw/day consisted of ↓ fetal wt. No litters were available for assessment at doses above.
Developmental Toxicity (gavage) NZW rabbit PMRA # 1889923	<u>Maternal</u> NOAEL = 10 mg/kg bw/day LOAEL was not established <u>Developmental</u> NOAEL = 10 mg/kg bw/day LOAEL was not established No evidence of sensitivity of the young.
In vitro Bacterial Gene Mutation Assay (*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2*hcr*) PMRA # 1889946	Negative
In vitro Mammalian Gene Mutation Assay – V79 Cells PMRA # 1889916	Negative
In vitro Chromosome Aberration Assay – CHO Cells Chinese Hamster Ovary cells PMRA # 1889945	Negative

Study Type/Animal/PMRA #	Study Results
In vivo Mammalian Cytogenetics – Erythrocyte Micronucleus Assay CD-1 Mouse PMRA # 1889924	Negative
Unscheduled DNA Synthesis (in vitro) HeLa S3 cells (Human cell line) PMRA # 1889918	Negative
Range-finding Acute Neurotoxicity (gavage) Range-finding Sprague-Dawley rat PMRA # 1889941	A NOAEL was not established as this was a dose range-finding study. No treatment-related effects.
Acute Neurotoxicity (gavage) Sprague-Dawley rat PMRA # 1889943	NOAEL = 2000 mg/kg bw LOAEL was not established.
90-Day Neurotoxicity (dietary) Sprague-Dawley rat PMRA # 1889943	NOAEL = 210 mg/kg bw/day (♂) NOAEL = 23 mg/kg bw/day (♀) LOAEL = 238 mg/kg bw/day (♀) Based on ↓bw & bwg. LOAEL = 439 mg/kg bw/day (♂) Based on ↓bw & bwg.
28-Day Immunotoxicity study (dietary) CD-1 mouse PMRA # 1957633	NOAEL = 70/68 mg/kg bw/day (AFC/NK group ♀s) LOAEL = 755/691 mg/kg bw/day Based on clinical signs (thin, unkempt appearance, ↓ defecation, yellow material on the mouth, ventral area, urogenital/anogenital area and limbs) in 1♀, bw loss (wk 1), ↓ overall bwg, ↓ thymus weight. No indication of selective immunotoxicity.

Study Type/Animal/PMRA #	Study Results
Metabolism and Toxicokinetics Fischer rat PMRA # 1889925	**Absorption:** Absorption was low (1-4% AD) and was similar between sexes and across dose groups. No radioactivity was observed in the bile following biliary cannulation, indicating that the compound in the feces represented unabsorbed kasugamycin. **Excretion:** Excretion was similar between sexes and dose groups. The majority of the dose was recovered within 48 hours from the feces (82-94%) and to a lesser degree from the urine (1.3-3.1%). At 168 hours post-dose fecal excretion accounted for 88-95% of administered radioactivity; urinary excretion accounted for 1.4-3.3%. Radioactivity concentrations in blood following a single oral dose were highest at 1 hour (T_{max}) post-dosing, with levels below the limit of quantitation by 24 hours. A terminal half-life of 1.17-1.55 hours was observed. The area under the curve (AUC) was not proportional to dose. Following a single high dose, the AUC was 6x and 4.5x higher than that following a single low dose in males and females, respectively. **Distribution:** Distribution was similar between sexes and across dose groups. At 1-6 hours post-dosing, concentrations of radioactivity in the kidneys, urinary bladder, lymph nodes and pancreas were elevated relative to blood levels. Radioactivity levels were also elevated in the uterus and liver (both sexes) at the last observation time point. In addition, radioactivity appeared to partition to the plasma. Radioactivity levels were below detection limits in all tissues except kidneys after 168 hours, with 0.11% of the administered dose (AD) retained in the carcass. For both the high and low dose groups, radioactivity measured in the tissues was reduced following repeated dosing, and therefore bioaccumulation of kasugamycin is not anticipated. **Metabolism:** Metabolites identified were similar between the sexes and dose groups. Only parent compound was identified in the feces. In addition to the parent compound, minor levels of the metabolite, kasuganobiosamine, were identified in the urine, plasma, and kidney. In the liver, trace amounts of radioactivity revealed what was most likely kasugamycin, kasuganobiosamine, and the intermediate metabolite, kasugamycinic acid. Identified metabolites were not quantified since adequate chromatographic separation of the parent and its metabolites could not be achieved. The biotransformation pathway of kasugamycin involved deamination/oxidation of the -C=N- bond to kasugamycinic acid, followed by decarboxylation/hydrolysis to yield kasuganobiosamine.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for kasugamycin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Not established as no appropriate endpoint warranting the setting of an acute reference dose.		
Repeated dietary	2 year chronic dietary study in the rat	NOAEL = 11 mg/kg bw/day LOAEL = 116 mg/kg bw/day Based on testicular effects (softening and atrophy), renal effects (increased relative wt and brown pigment deposition in the proximal tubular cells) increased cecal wt and foam cell aggregation in the lungs.	100
	ADI = 0.1 mg/kg bw/day		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short- to Intermediate -term dermal	21-day dermal study in the rat	NOAEL = 50 mg/kg bw/day LOAEL = 100 mg/kg bw/day Based on scabbing and reddening of skin, erythema, edema, pinpoint scabbing, brown discoloration, scarring, decreased thymus wt, minimal acanthosis and minimal acute inflammation of the skin	100
Long-term dermal[2]	2 year chronic dietary study in the rat	NOAEL = 11 mg/kg bw/day LOAEL = 116 mg/kg bw/day Based on testicular effects (softening and atrophy), renal effects (increased relative wt and brown pigment deposition in the proximal tubular cells) increased cecal wt and foam cell aggregation in the lungs.	100
Short- to Intermediate -term inhalation[3]	90-day dietary study in the rat	NOAEL = 18 mg/kg bw/day LOAEL = 58 mg/kg bw/day Based on red blood cell effects, ↑ cecal wt and ↑ eosinophilic bodies in proximal tubular cells of the kidneys in males.	100
Long-term inhalation[3]	2 year chronic dietary study in the rat	NOAEL = 11 mg/kg bw/day LOAEL = 116 mg/kg bw/day Based on testicular effects (softening and atrophy), renal effects (increased relative wt and brown pigment deposition in the proximal tubular cells) increased cecal wt and foam cell aggregation in the lungs.	100
Cancer	No evidence of carcinogenicity.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) was used in a route-to-route extrapolation

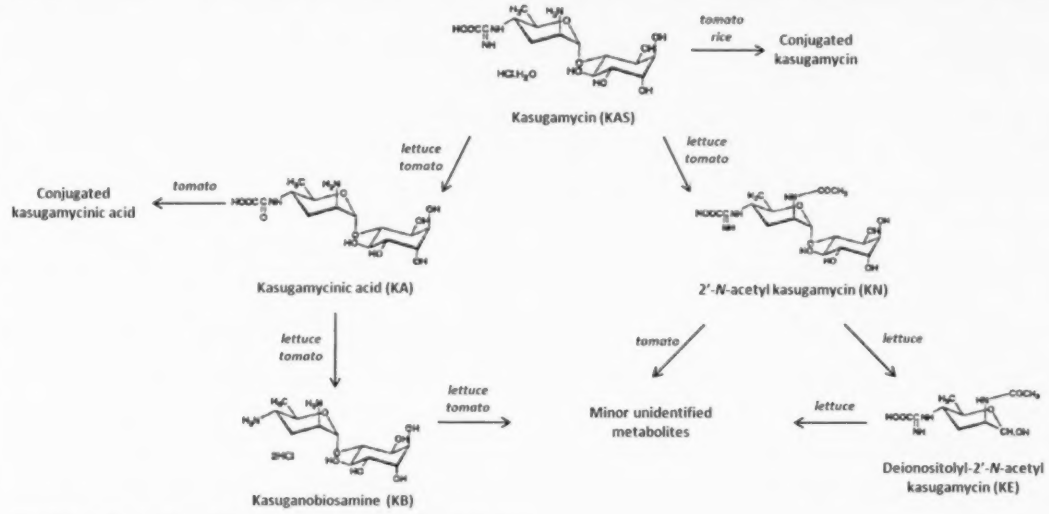
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 4 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN RICE		PMRA # 2033375
Radiolabel Position	**^{14}C(U)-hexopyranosyl-kasugamycin**	
Test Site	Pots maintained in glass greenhouses	
Treatment	Single foliar spray to rice plants	
Rate	452.7 g a.i./ha	
Timing	Approximatively at 50% of rice heading	
Preharvest interval	2-4 hours after treatment (i.e. 0 DAT), 7 DAT, 21 DAT and 47 DAT	
Average TRRs in rice forage were 6.80 ± 1.24 ppm (0 DAT); 4.75 ± 0.33 ppm (7 DAT) and 2.82 ± 0.55 ppm (21 DAT). In rice grain, average TRRs were 11.3 ± 4.1 ppm (0 DAT); 3.49 ± 1.55 ppm (7 DAT); 0.952 ± 0.326 ppm (21 DAT) and 0.481 ± 0.033 ppm (47 DAT). Average TRRs in rice hulls, kernels and straw, at maturity (47 DAT), were 1.69 ± 0.40 ppm; 0.212 ± 0.014 ppm and 6.94 ± 1.89 ppm, respectively. Average TRR levels in rice straw are much higher to those measured in 21-DAT rice forage. These results are probably due to dessication/drying of the straw at maturity. Extractable residues and PES in the rice matrices ranged from 89.5% to 105.4% and from 0.2 to 3.7%, respectively, with overall accountabilities ranging from 93.4% to 105.6%. Kasugamycin was the only identified residue and accounted for 58.6-82.3% of the TRRs (2.02-6.70 ppm) in rice forage; 39.3-94.0% of the TRRs (0.201-14.4 ppm) in rice grain; 30.6% of the TRRs (0.649 ppm) in rice hulls; 50.3% of the TRRs (0.113 ppm) in rice kernels and 54.9% of the TRRs (4.925 ppm) in rice straw. One minor degradation product (2-hydroxy-3-amino-6-methyl-2,3-dihydropyran) was identified in all rice samples and was due to degradation of kasugamycin under harsh acid conditions.		
Metabolites Identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**^{14}C(U)-hexopyranosyl**	**^{14}C(U)-hexopyranosyl**
Rice forage	Kasugamycin	--
Rice hull	Kasugamycin	--
Rice kernel	Kasugamycin	--
Rice grain	Kasugamycin	--
NATURE OF THE RESIDUE IN LETTUCE		**PMRA # 2033374**
Radiolabel Position	**^{14}C(U)-hexopyranosyl-kasugamycin**	
Test Site	Crates maintained in an aluminum framed greenhouse	
Treatment	Single foliar spray to lettuce plants	
Rate	225 g a.i./ha	
Timing	At BBCH growth stage 45 (when plants were ca. 50% of the expected mature head size)	
Preharvest interval	2-4 hours after treatment (i.e. 0 DAT), 7 DAT and 14 DAT	
Average TRRs in lettuce foliage were 5.728 ± 0.444 ppm (0 DAT); 2.414 ± 0.280 ppm (7 DAT) and 1.775 ± 0.510 ppm (14 DAT). Extractable residues and PES in the lettuce foliage were ca. 89.2-99.1% and 0.3-1.2%, respectively, with overall accountabilities of 100%. Kasugamycin was the predominant identified residue and accounted for 72.7-86.2% of the TRRs (1.146-4.941 ppm). Four minor metabolites were identified in lettuce foliage: deionositolyl-2′-*N*-acetyl kasugamycin, kasugamycinic acid, 2′-*N*-acetyl kasugamycin and kasuganobiosamine, each accounting for < 10% of the TRRs (0.028-0.124 ppm).		
Metabolites Identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**^{14}C(U)-hexopyranosyl**	**^{14}C(U)-hexopyranosyl**
Lettuce foliage	Kasugamycin	Deionositolyl-2′-*N*-acetyl kasugamycin; Kasugamycinic acid; 2′-*N*-Acetyl kasugamycin; Kasuganobiosamine

NATURE OF THE RESIDUE IN TOMATO		PMRA # 1889904
Radiolabel Position	**^{14}C(U)-hexopyranosyl-kasugamycin**	
Test Site	Plastic crates maintained in a greenhouse	
Treatment	Single foliar spray to tomato plants	
Rate	189 g a.i./ha	
Timing	ca. 18 weeks after planting	
Preharvest interval (DAT)	2-4 hours after treatment (i.e. 0 DAT), 1 DAT, 7 DAT, 14 DAT, 21 DAT, 28 DAT	
TRRs in tomato foliage were 2.865 ppm (0 DAT); 4.732 ppm (1 DAT); 1.774 ppm (7 DAT); 2.925 ppm (14 DAT); 2.570 ppm (21 DAT) and 4.287 ppm (28 DAT). TRRs in tomato fruit were 0.011 ppm (0 DAT); 0.008 ppm (1 DAT); 0.027 ppm (7 DAT); 0.072 ppm (14 DAT); 0.098 ppm (21 DAT) and 0.084 ppm (28 DAT). Extractable residues and PES in the tomato foliage were 87.7-89.7% and 10.3-12.4%, respectively, with overall accountabilities of 100%. Extractable residues and PES in the tomato fruit were 91.0-94.1% and 5.9-9.0%, respectively, with overall accountabilities of 100%. Kasugamycin was the predominant identified residue and accounted for 57.3-93.9% of the TRRs (0.007-0.049 ppm) in tomato fruit and 52.5-84.0% of the TRRs (1.23-2.40 ppm) in tomato foliage. Three minor metabolites were identified in tomato fruit or foliage: kasugamycinic acid, 2′-*N*-acetyl kasugamycin and kasuganobiosamine, each accounting for < 10% of the TRRs (0.009-0.304 ppm) except for kasugamycinic acid in the 28-DAT tomato fruit which accounted for 12% of the TRRs (0.010 ppm).		
Metabolites Identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**^{14}C(U)-hexopyranosyl**	**^{14}C(U)-hexopyranosyl**
Tomato fruit	Kasugamycin	Kasugamycinic acid
Tomato foliage	Kasugamycin	Kasugamycinic acid; 2′-*N*-Acetyl kasugamycin; Kasuganobiosamine

CONFINED ACCUMULATION IN ROTATIONAL CROPS – LETTUCE, RADISH, WHEAT		PMRA # 1890014
Radiolabel Position	**[D-glucosamine-U-^{14}C]-kasugamycin**	
Test site	Outdoors	
Formulation used for trial	Aqueous and slightly acidic solution	
Rate	191-200 g a.i./ha	
Timing	30, 120 and 365 days prior to planting lettuce, radish and wheat; the 365-day lettuce crop was destroyed by pests and replanted 427 days after soil treatment.	
TRRs in lettuce were 0.012 ppm (30-day PBI); 0.009 ppm (120-day PBI) and 0.002 ppm (427-day PBI). TRRs in radish roots were 0.005 ppm (30-day PBI); 0.003 ppm (120-day PBI) and 0.001 ppm (365-day PBI). TRRs in radish tops were 0.006 ppm (30-day PBI); 0.004 ppm (120-day PBI) and 0.006 ppm (365-day PBI). TRRs in wheat forage were 0.022 ppm (30-day PBI); 0.011 ppm (120-day PBI) and 0.005 ppm (365-day PBI). TRRs in wheat hay were 0.037 ppm (30-day PBI); 0.011 ppm (120-day PBI) and 0.07 ppm (365-day PBI). TRRs in wheat grain were 0.015 ppm (30-day PBI); 0.006 ppm (120-day PBI) and 0.005 ppm (365-day PBI). TRRs in wheat straw were 0.056 ppm (30-day PBI); 0.003 ppm (120-day PBI) and 0.017 ppm (365-day PBI). Samples with TRRs at or above 0.01 ppm were extracted for characterization and identification of radioactive residues. Kasugamycin was the predominant identified residue and accounted for 4.5-14.3% of the TRRs (0.001-0.006 ppm) in lettuce and wheat grain (30-day PBI); wheat forage (30- and 120-day PBIs); wheat hay (120- and 365-day PBIs) and wheat straw (30-, 120- and 365-day PBIs). One minor metabolite was identified in wheat hay: kasugamycinic acid which accounted for < 10% of the TRRs (0.001 ppm). Based on these results, no field accumulation study is required. Further to this, no plant-back interval is required.		
Metabolites Identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Matrix / **PBI (days)**	**[D-glucosamine-U-^{14}C]-kasugamycin**	**[D-glucosamine-U-^{14}C]-kasugamycin**
Lettuce / 30	Kasugamycin	---
Wheat forage / 30, 120	Kasugamycin	---
Wheat hay / 120, 365	Kasugamycin	Kasugamycinic acid
Wheat grain / 30	Kasugamycin	---
Wheat straw / 30, 120, 365	Kasugamycin	---



Proposed metabolic scheme in tomato, lettuce and rice

The metabolic pathways in lettuce, rice (forage, grain, straw, kernel, hull) and tomato (foliage, fruit) appeared to be similar and consist of the metabolic degradation of kasugamycin by conversion to form kasugamycinic acid. Conversion of the parent compound to 2′-*N*-acetyl kasugamycin by acetylation was considered a minor degradation pathway. Minor metabolites were also formed by bond cleavage (deionositolyl-2′-N-acetyl kasugamycin, kasuganobiosamine). Conjugation of the parent and kasugamycinic acid also occurred. The metabolic pathways in rotational crops (radish roots and tops; lettuce; wheat forage, hay, grain and straw) appeared similar and was consistent with the ones observed in primary crops. Kasugamycin was the predominant residue. Only one minor metabolite was identified in wheat hay as kasugamycinic acid.

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA # 1889892

A lactating goat was dosed orally by capsule with [D-glucosamine-U-^{14}C]-kasugamycin at a dose equivalent to 10.8 ppm in the diet (equivalent to 12.6 ppm based on a dry weight of feed or 29.8 mg a.i./day) for five consecutive days. Milk was collected twice daily throughout the study period. Urine and feces samples were collected once daily throughout the study period. Blood and cage rinses were collected 5 hours after the last dose. The lactating goat was sacrificed 5 hours after administration of the final dose. Samples of tissues (i.e. muscle (loin and flank), fat (renal, omental and subcutaneous), liver, kidneys, entire gastrointestinal (GI) tract with contents and bile) were collected after sacrifice. TRRs in the urine, cage wash, bile, skim milk and milk fat subsamples were determined by LSC. Feces, GI tract and blood samples were analysed by combustion. Muscle, fat, liver and kidney samples were first digested with a tissue solubilizer, incubated overnight and then analyzed by LSC.

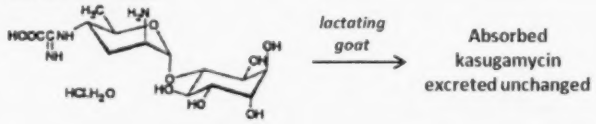
TRRs (expressed as kasugamycin equivalents) in skim milk were constant from Day 1 (PM) to Day 5 (PM) with levels ranging between 0.001-0.003 ppm. In milk fat, TRRs reached a maximum at Day 2 (AM) and were constant from Day 2 (PM) to Day 5 (PM) with levels ranging from 0.009-0.014 ppm. In feces and urine, TRRs reach a maximum at Day 4. The majority of residues in kidney, liver and renal fat samples were extractable (92.9-96.0% of the TRRs) with 3.95-7.14% of the TRRs (0.001-0.010 ppm) remaining as unextractable residues (PES). Samples with TRRs at or above 0.01 ppm were extracted for characterization and identification of radioactive residues. Kasugamycin was the predominant identified residue and accounted for ca. 90-100% of the TRRs (0.012-0.235 ppm). No metabolites were identified.

Matrices	**[D-glucosamine-U-^{14}C]-kasugamycin**	
	% of Administered Dose	**TRRs (ppm)**
Urine and feces	56.40	52.28
GI tract	24.48	3.652
Muscle (loin)	< 0.01	0.003
Muscle (flank)	< 0.01	0.003

Fat (renal)	< 0.01	0.012
Fat (omental)	< 0.01	0.002
Fat (subcutaneous)	< 0.01	0.007
Kidney	0.02	0.262
Liver	0.01	0.013
Milk fat	< 0.01	0.13
Skim milk	0.01	0.02

Metabolites identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**[D-glucosamine-U-^{14}C]-kasugamycin**	**[D-glucosamine-U-^{14}C]-kasugamycin**
Kidney	Kasugamycin	---
Liver	Kasugamycin	---
Renal fat	Kasugamycin	---

Proposed Metabolic Scheme in Livestock



Kasugamycin (KAS)

STORAGE STABILITY	**PMRA # 1890008-1890011; 1890026-1890027; 2136698**

Residues of kasugamycin were shown to be stable between -40°C and -0.2°C for 23.5 months in pepper RAC; 33.0 months in tomato RAC; 23.2 months in tomato paste; 22.8 months in tomato puree; 10.1 months in apple RAC; 6.5 months in apple juice; 6.7 months in apple pomace; 7.7 months in pear RAC and 28.2 months in walnut nutmeat. Samples of pear (RAC) were stored for longer storage intervals than the demonstrated ones. Preliminary storage stability data were received for tomato (RAC, puree, paste) and walnut (nutmeat). The final reports for pear (RAC), tomato (RAC, paste, puree) and walnut (nutmeat) are required as a condition of registration of kasugamycin.

CROP FIELD TRIALS ON FRUITING VEGETABLES	PMRA # 1890010-1890011; 1890026-1890027

Twelve tomato field trials were conducted in NAFTA representative regions 1 (1 trial), 3 (2 trials), 5 (1 trial), 6 (2 trials) and 10 (6 trials) during the 2001-2002, 2007 and 2009 growing seasons. Five tomato trials were also conducted in greenhouses in NAFTA representative regions 2 (2 trials), 3 (1 trial), 9 (1 trial) and 12 (1 trial) during the 2007 or 2009 growing seasons. Thirteen pepper (bell and non-bell) field trials were conducted in NAFTA representative regions 2 (2 trials), 3 (2 trials), 5 (2 trials), 6 (5 trials) and 10 (2 trials) during the 2001-2002 and 2007 growing seasons. Two pepper (bell) trials were also conducted in greenhouses in NAFTA representative regions 2 (1 trial) and 8 (1 trial) during the 2007 growing season.

Tomatoes and peppers were treated with three foliar (directed or broadcast) applications of a liquid formulation at total application rates of 56.3-58.2 g a.i./ha or 69.4-80.0 g a.i./ha equivalent to 0.78- to 1.05-fold maximum seasonal approved GAP. No adjuvants were added to the spray mixtures for any of the applications. In one tomato field trial, an additional plot of tomatoes was treated with three foliar applications at a total application rate of 290.2 g a.i./ha equivalent to four-fold maximum seasonal approved GAP. In one of the tomato greenhouse trials, an additional plot was treated with three drench applications to the roots of the tomatoes at total application rate of 29.9 g a.i./100 L water. Samples of tomato and pepper fruit were harvested 0-1 day after the last treatment. Residue decline samples of tomato were also harvested at the two greenhouse sites and at one field site at PHIs of 0 day; 3-4 days; 7 days; 13-14 days and/or 19-20 days. Residue decline samples of pepper were also harvested at one field site at PHIs of 0 day; 3 days and 7 days.

Commodity	Total Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Tomato – field trials	56.3-74.5	**0-1**	**28**	**< 0.040**	**< 0.040**	**0.040**	**0.040**	**0.040**	**0**
		3	4	< 0.040	< 0.040	0.040	0.040	0.040	0
		7	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
	290.2	1	2	0.0439	0.0556	0.0498	0.0498	0.0498	NA
		3	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
Tomato – greenhouse trials	69.8-77.0	**0-1**	**10**	**< 0.040**	**0.0728**	**0.0727**	**0.0400**	**0.0483**	**0.0140**
		3-4	4	< 0.040	< 0.040	0.040	0.040	0.040	0
		7	4	< 0.040	< 0.040	0.040	0.040	0.040	0
		13-14	4	< 0.040	< 0.040	0.040	0.040	0.040	0
		19-20	4	< 0.040	< 0.040	0.040	0.040	0.040	0
Tomato – drench appl./greenhouse	29.9 g a.i./ 100 L H_2O	0	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
Bell pepper – field trials	56.5-80.0	0	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		1	**14**	**< 0.040**	**< 0.040**	**0.040**	**0.040**	**0.040**	**0**
		3	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		7	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
Bell pepper – greenhouse trials	69.8-74.8	**1**	**4**	**0.0418**	**0.0647**	**0.0588**	**0.0476**	**0.0504**	**0.0108**
Non-bell pepper – field trials	56.5-80.0	**1**	**14**	**< 0.040**	**0.107**	**0.0837**	**0.0400**	**0.0462**	**0.0183**

CROP FIELD TRIALS ON POME FRUITS	PMRA # 1890009; 2136698

Fifteen apple field trials were conducted in NAFTA representative regions 1 (4 trials), 2 (2 trials), 5 (3 trials), 9 (1 trial), 10 (1 trial) and 11 (4 trials) during the 2007 growing season. Side-by-side trials were also conducted in NAFTA representative regions 5 (4 trials) and 11 (1 trial) during the 2007 growing season to determine the effects of surfactant on the magnitude of the residues of kasugamycin. Three pear field trials were conducted in NAFTA representative region 5 during the 2010 growing.

Apples and pears were treated with four foliar directed applications of Kasumin 2L at total application rates of 292.5-382.2 g a.i./ha equivalent to ca. 0.72- to 0.94-fold maximum seasonal approved GAP. All apple and pear field trials were conducted with a surfactant except the side-by-side apple field trials which were conducted with and without a surfactant. Samples of apple and pear fruits were harvested 87-100 days after the last treatment. Apple and pear residue decline samples were also harvested at PHIs of 32, 46, 60 and 75 days for apples and 27-29 days for pears.

Commodity	Total Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Apple – with adjuvant	292.5-382.2	32	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		46	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		60	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		75	2	< 0.040	< 0.040	0.040	0.040	0.040	NA
		90-100	**40**	**< 0.040**	**0.075**	**0.068**	**0.040**	**0.043**	**0.007**
Apple – without adjuvant	364.3-382.2	**91-94**	**10**	**< 0.040**	**< 0.040**	**0.040**	**0.040**	**0.040**	**0**
Pear – with adjuvant	381.1	27-29	6	0.091	0.203	0.193	0.117	0.134	0.047
		87-92	**6**	**< 0.040**	**0.092**	**0.087**	**0.052**	**0.060**	**0.022**

CROP FIELD TRIALS ON WALNUTS	PMRA # 1890008

Three walnut field trials were conducted in NAFTA representative region 10 during the 2007 growing season. Walnuts were treated with four foliar directed applications of Kasumin 2L at application rates of 92.5-97.6 g a.i./ha/appl. and RTIs of 6-8 days for total application rates of 375.5-381.1 g a.i./ha equivalent to ca. 0.93-fold maximum seasonal approved GAP. No adjuvant was added to the spray mixtures at any trial. Walnuts were harvested at PHIs of 98-110 days.

Commodity	Total Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Walnut	375.5-381.1	**98-110**	**6**	**< 0.040**	**0.040**	**0.040**	**0.040**	**0.040**	**0**

PROCESSED FOOD AND FEED	PMRA # 1890009-1890010

Processing studies were conducted on tomatoes and apples. Tomatoes were treated with three foliar applications of kasugamycin (liquid formulation) at application rates of 23.3 g a.i./ha and RTIs of 7 days for a total application rate of 69.9 g a.i./ha/appl. equivalent to 0.95-fold the maximum seasonal approved GAP. Apples were treated with five foliar applications of kasugamycin (liquid formulation) at application rates of 92.5-94.5 g a.i./ha/appl. and RTIs of 7 days between the first four applications and 98 days between the fourth and fifth (last) application for a total application rate of 467.4 g a.i./ha equivalent to 1.15-fold maximum seasonal proposed GAP. Residues of kasugamycin were below the LLMV of 0.04 ppm in all raw agricultural commodities and in tomato puree, tomato paste and apple pomace. Quantifiable residues were found in apple juice yielding a processing factor of 1.25-fold.

LIVESTOCK FEEDING	PMRA # —

The only feed item is apples (processed into wet apple pomace), which is considered an "alternative feedstuff" for dairy cattle only. There are no poultry feed items among the requested crops. Maximum residues in apple pomace were estimated to be 0.068 ppm (HAFT × experimental PF = 0.068 ppm × 1).

The dietary burden determined using the Maximum Reasonable Balanced Diet calculator (Version A) was calculated to be 0.017 ppm for dairy cattle. Therefore, no quantifiable residues of kasugamycin are expected in dairy cattle tissues or milk from feeding wet apple pomace processed from treated apples according to the Canadian use pattern. As a result, feeding studies are not required at this time.

Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (rice, lettuce, tomato)** **Rotational crops (lettuce, radish, wheat)**		Kasugamycin Kasugamycin	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (rice, lettuce, tomato)** **Rotational crops (lettuce, radish, wheat)**		Kasugamycin Kasugamycin	
METABOLIC PROFILE IN DIVERSE CROPS		The metabolic profile is similar in rice, lettuce and tomato.	
ANIMAL STUDIES			
ANIMALS		**Ruminant**	
RESIDUE DEFINITION FOR ENFORCEMENT		Kasugamycin	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Kasugamycin	
METABOLIC PROFILE IN ANIMALS		The metabolic profile was determined in lactating goat.	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary risk **ADI = 0.1 mg/kg bw** **Estimated chronic drinking water concentration = 1.6 µg a.i./L**	All infants < 1 year	1.9	2.0
	Children 1–2 years	2.9	3.0
	Children 3 to 5 years	2.0	2.0
	Children 6–12 years	0.9	0.9
	Youth 13–19 years	0.5	0.5
	Adults 20–49 years	0.4	0.4
	Adults 50+ years	0.3	0.4
	Total population	0.6	0.6

Table 6 Fate and Behaviour in the Environment

Property	Test substance	Value[1]		Comments	PMRA #
Abiotic transformation					
Hydrolysis	Kasugamycin	Half-life at 25°C: pH 5: 678 d (SFO) pH 7: 77.9 d (SFO) pH 9: 11.4 d (SFO)		Is an important route of transformation at environmental relevant pHs.	1889938
Photo-transformation in water	Kasugamycin	Half-life at 25°C: Sterile buffer: 436 d (SFO) Sterile lake water: 8.2 d (SFO)		Not expected to be an important route of dissipation	1889891
Photo-transformation on soil	Request for a waiver submitted and granted based on results of other studies. Not expected to be an important route of transformation.				1889970
Photo-transformation in air	Kasugamycin is not volatile under field conditions based on vapour pressure and Henry's law constant. A study is not required for Kasugamycin.				
Biotransformation					
Biotransformation in aerobic soil	Kasugamycin	DT_{50}: 39.5 d (IORE) DT_{90}: 162 d Estimated first-order DT_{50}, calculated using $DT_{90} \times 0.301$: **48.9 d**		Moderately persistent, based on Goring *et al.* (1975)	1889944
Biotransformation in anaerobic soil	Kasugamycin	This study did not fulfill the data requirements as anaerobicity was not maintained in the flooded soil.			1889956
Biotransformation in aerobic water systems North Dakota Loamy sand soil (pH 8.1; 1.2% OC) + Lake water (pH 8.1; OC: not available)	Kasugamycin	Lake water/ Loamy sand soil sediment system	***Water*** DT_{50}: 7.0 d (SFO) DT_{90}: 23.4 d ***Sediment*** DT_{50}: 156 d (SFO) DT_{90}: 517 d ***Entire system*** DT_{50}: 18.2 d (IORE) DT_{90}: 179 d Estimated first-order DT_{50} calculated from $DT_{90} \times 0.301$: **53.9 d**	Moderately persistent	1889893
North Dakota Clay loam soil (pH 8.0; 3.1% OC) + River water (pH: 7.8; %OC not available)		River water/ Clay loam soil sediment system	***Water*** DT_{50}: 7.0 d (SFO) DT_{90}: 23.5 d ***Sediment*** DT_{50}: 108 d (SFO) DT_{90}: 358 d ***Entire system*** DT_{50}: 28.6 d (SFO) DT_{90}: 95 d	Slightly persistent	

Biotransformation in anaerobic water systems Louisiana Clay loam soil (pH 6.5;1.33% OC) + Wisconsin Well water (pH 7.7; % OC not available)	Kasugamycin	Well water/ Clay loam soil sediment system	***Water*** Not determined ***Sediment*** Not determined ***Entire system*** DT_{50}: 170 d (SFO) DT_{90}: 566 d	Moderately persistent	1889957
Mobility					
Adsorption / desorption in soil	Kasugamycin	North Dakota sandy clay loam	K_d = 4.4 mL/g; K_{OC} = 130 mL/g	High mobility	1889896
		North Dakota clay loam	K_d = 10.4 mL/g; K_{OC} = 316 mL/g	Moderate mobility	
		North Dakota sandy loam	K_d = 3.3 mL/g; K_{OC} = 300 mL/g	Moderate mobility	
		Florida sand	K_F = 0.03 mL/g; K_{FOC} = 6.4 mL/g	Very high mobility	
Soil column leaching	Kasugamycin	Light clay	K_{OC} = 1394 mL/g	Low mobility	1889953
		Sandy clay loam	K_{OC} = 1000 mL/g	Low mobility	
		Loam	K_{OC} = 1495 mL/g	Low mobility	
	Kasugamycinic acid	Light clay	K_{OC} = 339 mL/g	Moderately mobile	
	Kasugano-biosamine	Light clay	K_{OC} = 6605 mL/g	Immobile	
Field studies					
Field dissipation in four U.S. soils	Kasugamycin	California, Washington, New York, Georgia	This study was found supplemental. No half-life could be determined.		1890012

1 Kinetics models: DFOP = Double first-order in parallel; SFO = single first-order; IORE = indeterminate order rate equation.

Table 7 Screening level EECs for kasugamycin in soil, water, and plants based on four direct cumulative applications of 102 g a.i./ha (7-day intervals) for pome fruits

Environmental Compartment	Half-life (days)	EEC (units)	Assessment Group
Soil with incorporation to a 15 cm depth	48.9[a]	0.15 mg a.i./kg dw soil	Earthworms
Soil with no incorporation	48.9	353.76 g a.i./ha	Terrestrial plants (seedling emergence endpoints only)
15-cm Deep water body	53.9[b]	0.239 mg a.i./L	Amphibians
80-cm Deep water body	53.9	0.045 mg a.i./L	Aquatic organisms other than amphibians
Plant foliage	10.0[c]	227.25 g a.i./ha	Bees, Terrestrial plants (vegetative vigour endpoints only)

[a] Aerobic soil estimated first-order DT_{50}
[b] Aerobic water estimated first-order DT_{50}
[c] Default foliar half-life

Table 8 Screening level EECs for kasugamycin in vegetation and insects after four direct cumulative applications of 102 g a.i./ha (7-day intervals) for pome fruits

Food item	EEC (mg a.i./kg fw)[a]		Fresh / dry weight ratios	EEC (mg a.i./kg dw)	
	Maximum Residues	Mean Residues		Maximum Residues	Mean Residues
Short range grass	48.63	17.27	3.3[b]	160.49	57.00
Long grass	22.27	7.27	4.4[b]	97.99	32.00
Forage crops	27.50	9.09	5.4[b]	148.49	49.09
Small insects	11.82	6.59	3.8[c]	44.91	25.04
Large insects	2.95	1.41	3.8[c]	11.23	5.35
Grain and seeds	2.95	1.41	3.8[c]	11.23	5.35
Fruit	2.95	1.41	7.6[c]	22.45	10.70

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified by Fletcher *et al.* (1994)
[b] Fresh / dry weight ratios from Harris (1975)
[c] Fresh / dry weight ratios from Spector (1956)

Table 9 Toxicity of Kasugamycin to non-target terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm (*Eisenia fetida*)	14-day Acute	TGAI 71.5% free base	EC_{50}: > 1000 mg a.i/kg dw soil	No classification	1889952
Bee (*Apis mellifera*)	72-hour Acute Contact	TGAI 71.5% free base	LD_{50}: > 100 µg a.i./bee equivalent to > 112 kg a.i./ha	Relatively non-toxic	1889967
	96-hour Acute Oral	TGAI 71.5% free base	LD_{50}: 30.3 µg a.i./bee equivalent to 33.9 kg a.i./ha	Relatively non-toxic	1889968
Birds					
Bobwhite quail (*Colinus virginianus*)	Acute	TGAI 73.9% free base	LD_{50}: > 2000 mg a.i./kg bw NOEL : 2000 mg a.i./kg bw (highest dose tested)	Practically non-toxic	1889862
	5-day Dietary	TGAI 73.9% free base	LC_{50}: > 5000 mg a.i./kg diet, equivalent to an **LD_{50} > 982.7 mg a.i./kg bw/day** NOEC: 5000 mg a.i./kg diet (highest concentration tested), equivalent to a **NOEL of 982.7 mg a.i./kg bw/day**	Practically non-toxic	1889860
	25-week Reproduction	TGAI 70.3% free base	NOEC: 1000 mg a.i./kg diet (highest concentration tested), equivalent to a **NOEL of 90.2 mg a.i./kg bw/day**	No classification	1889888
Mallard duck (*Anas platyrhynchos*)	Acute	TGAI 73.9% free base	LD_{50}: > 2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw (highest dose tested)	Practically non-toxic	1889861
	5-day Dietary	TGAI 73.9% free base	LC_{50}: > 5000 mg a.i./kg diet, equivalent to an **LD_{50} > 1118.9 mg a.i./kg bw/day** NOEC: 5000 mg a.i./kg diet (highest concentration tested), equivalent to a **NOEL of 1118.9 mg a.i./kg bw/day**	Practically non-toxic	1889859

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
	21-week Reproduction	TGAI 70.3% free base	NOEC: 1000 mg a.i./kg diet (highest concentration tested), equivalent to a **NOEL of 101.4 mg a.i./kg bw/day**	No classification	1889885
Zebra Finch (*Taeniopygia guttata*)	Acute	TGAI 70.3% free base	LD_{50}: > 2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw (highest dose tested)	Practically non-toxic	1889863
Vascular plants					
Allium cepa (onion), *Lolium perenne* (ryegrass), *Triticum aestivum* (wheat), *Zea mays* (corn), *Beta vulgaris* (sugarbeet), *Glycine max* (soybean), *Lactuca sativa* (lettuce), *Linum usitatissimum* (flax), *Lycopersicon esculentum* (tomato), *Raphanus sativus* (radish)	21-day Seedling emergence	EP 2.18% free base	ER_{25} < 98.15 g a.i./ha (based on effects on wheat, highest rate tested) Onion: 37% reduction in shoot dry weight Wheat: 26% reduction in shoot dry weight		1889966
	21-day Vegetative vigour	EP 2.18% free base	ER_{25} > 98.15 g a.i./ha (highest concentration tested) Tomato: 9% reduction in shoot dry weight Wheat and corn: 5% reduction in shoot dry weight		1889969
Mammals					
Rat	Acute	TGAI	LD_{50} > 5000 mg a.i./kg bw NOEL: 5000 mg a.i./kg bw (highest dose tested)	Practically non-toxic	1889905
	Reproduction	TGAI 80.6%	<u>Parental effects</u> NOAEL: 13.7 mg a.i./kg bw/day (♂) (based on decreased body weights and body weight gains in males) <u>Reproductive effects</u> NOAEL: 70.3 /82.9 mg a.i./kg bw/day (♂/♀) based on ↓ fertility and fecundity (F1 parents) and ↑ pre-coital interval (F1 parents - 2nd litter)	No classification	1889911

[a] Atkins *et al.* (1981) for bees and USEPA classification for others, where applicable

Table 10 Screening level risk assessment for non-target terrestrial organisms (other than birds and small mammals)

Organism	Exposure	Endpoint value with uncertainty factor, when applicable	EEC	RQ	LOC[a] Exceeded?
Invertebrates					
Earthworm (*E. fetida*)	14-day Acute	0.5x EC_{50} > 500 mg a.i/kg dw soil	0.15 mg a.i./kg soil	< 0.0003	No
Bee (*A. mellifera*)	72-hour Acute Contact	LD_{50} > 112 kg a.i./ha	227.25 g a.i./ha	< 0.0020	No
	96-hour Acute Oral	LD_{50} = 33.9 kg a.i./ha	227.25 g a.i./ha	0.0067	No
Vascular plants					
A. cepa (onion), *L. perenne* (ryegrass), *T. aestivum* (wheat), *Z. mays* (corn), *B. vulgaris* (sugarbeet), *G. max* (soybean), *L. sativa* (lettuce), *L. usitatissimum* (flax), *L. esculentum* (tomato), *R. sativus* (radish)	21-day Seedling emergence	ER_{25} < 98.15 g a.i./ha (based on effects on wheat and onion)	In-field: 353.76 g a.i./ha	> 3.60	**Yes**
	21-day Vegetative vigour	ER_{25} > 98.15 g a.i./ha (no effects found at that application rate)	In-field: 227.25 g a.i./ha	< 2.32[b]	**Yes**

[a] The level of concern (LOC) is 1.0.

[b] An ER_{25} > 98.15 g a.i./ha was used to calculate the RQ as a conservative estimate.

Table 11 Screening level risk assessment for birds and small mammals

Study type	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[a] (mg a.i./kg bw)	Risk Quotient	LOC[b] Exceeded?
Small Bird (0.02 kg)					
Acute	200.00	Insectivore (small insects)	11.45	< 0.06	No
Reproduction	90.20	Insectivore (small insects)	11.45	0.13	No
Medium Sized Bird (0.1 kg)					
Acute	200.00	Insectivore (small insects)	8.94	< 0.04	No
Reproduction	90.20	Insectivore (small insects)	8.94	0.10	No
Large Sized Bird (1 kg)					
Acute	200.00	Herbivore (short grass)	9.32	< 0.05	No
Reproduction	90.20	Herbivore (short grass)	9.32	0.10	No

Study type	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[a] (mg a.i./kg bw)	Risk Quotient	LOC[b] Exceeded?
Small Mammal (0.015 kg)					
Acute	500.00	Insectivore (small insects)	6.59	< 0.01	No
Reproduction	70.30	Insectivore (small insects)	6.59	0.09	No
Medium Sized Mammal (0.035 kg)					
Acute	500.00	Herbivore (short grass)	20.63	< 0.04	No
Reproduction	70.30	Herbivore (short grass)	20.63	0.29	No
Large Sized Mammal (1 kg)					
Acute	500.00	Herbivore (short grass)	11.03	< 0.02	No
Reproduction	70.30	Herbivore (short grass)	11.03	0.16	No

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[b] The level of concern (LOC) is 1.0.

Table 12 Refined risk assessment for non-target terrestrial plants

Organism	Exposure	Endpoint value	EEC	RQ	LOC[a] Exceeded?
A. cepa (onion), *L. perenne* (ryegrass), *T. aestivum* (wheat), *Z. mays* (corn), *B. vulgaris* (sugarbeet), *G. max* (soybean), *L. sativa* (lettuce), *L. usitatissimum* (flax), *L. esculentum* (tomato), *R. sativus* (radish)	21-day Seedling emergence	ER_{25} < 98.15 g a.i./ha (based on effects on wheat and onion)	Off-field (Early season airblast application, 74% spray drift): 261.78 g a.i./ha	> 2.67	**Yes**
	21-day Vegetative vigour	ER_{25} > 98.15 g a.i./ha (no effects found at that application rate)	Off-field (Early season airblast application, 74% spray drift): 168.17 g a.i./ha	< 1.71	Not expected to pose a risk

[a] The level of concern (LOC) is 1.0.

Table 13 Toxicity of kasugamycin to non-target aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Freshwater species					
Daphnia magna	48-hour Acute	TGAI 73.0% free base	LC_{50} > 66.2 mg a.i./L NOEC = 66.2 mg a.i./L (highest concentration tested)	Slightly toxic	1889890
	21-day Chronic	TGAI 63.4% free base	NOEC = 50 mg a.i./L (adult body length and reproductive effects)	No classification	1889950
Rainbow trout (*Oncorhynchus mykiss*)	96-hour Acute	TGAI 71.5% free base	LC_{50} > 120 mg a.i./L NOEC = 120 mg a.i./L (highest concentration tested)	Practically non-toxic	1889878
Fathead minnow (*Pimephales promelas*)	96-hour Acute	TGAI 71.5% free base	LC_{50} > 110 mg a.i./L NOEC = 110 mg a.i./L (highest concentration tested)	Practically non-toxic	1889877
	32-day Chronic ELS	TGAI 71.5% free base	NOEC = 9.5 mg a.i./L (highest concentration tested)	No classification	1889884
Green algae (*Pseudokirchneriella subcapitata*)	96-hour Acute	TGAI 71.5% free base	E_yC_{50} = 3.3 mg a.i./L EC_{50} = 4.2 mg a.i./L (cell density) E_rC_{50} = 14 mg a.i./L	No classification	1889867
Blue-Green algae (*Anabaena flos-aquae*)	96-hour Acute	TGAI 71.5% free base	E_yC_{50} = 0.76 mg a.i./L EC_{50} = 0.76 mg a.i./L (cell density) E_rC_{50} = 1.3 mg a.i./L	No classification	1889875
Diatom (*Navicula pelliculosa*)	96-hour Acute	TGAI 71.5% free base	E_yC_{50} = 90 mg a.i./L EC_{50} = 90 mg a.i./L (cell density) E_rC_{50} > 110 mg a.i./L	No classification	1889869
Vascular plant (*Lemna gibba*)	7-day Dissolved	TGAI 71.5% free base	E_yC_{50} = 85 mg a.i./L (frond density)	No classification	1889864
Marine species					
Mysid shrimp (*Americamysis bahia*)	96-hour Acute	TGAI	LC_{50} > 100 mg a.i./L NOEC = 100 mg a.i./L (highest concentration tested)	Practically non-toxic	1889881
Eastern oyster (*Crassostrea virginica*)	96-hour Acute (shell deposition)	TGAI	LC_{50} > 110 mg a.i./L EC_{50} > 110 mg a.i./L (shell growth) NOEC = 8.7 mg a.i./L (shell growth)	Practically non-toxic	1889883

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Sheepshead minnow (*Cyprinodon variegatus*)	96-hour Acute	TGAI 71.5% free base	LC_{50} > 110 mg a.i./L NOEC = 110 mg a.i./L (highest concentration tested)	Practically non-toxic	1889876
Diatom (*Skeletonema costatum*)	96-hour Acute	TGAI 71.5% free base	E_yC_{50} > 94 mg a.i./L EC_{50} > 94 mg a.i./L (cell density) E_rC_{50} > 94 mg a.i./L	No classification	1889871

[a] USEPA classification, where applicable

Table 14 Screening level risk assessment on non-target aquatic organisms

Organism	Exposure	Endpoint value with uncertainty factor, when applicable	EEC (mg a.i./L)	RQ	LOC Exceeded?
Freshwater species					
Daphnia magna	48-hour Acute	0.5x LC_{50}: > 33.1 mg a.i./L	0.045	< 0.0014	No
	21-day Chronic	NOEC: 50 mg a.i./L	0.045	0.0009	No
Rainbow trout (*O. mykiss*)	96-hour Acute	0.1x LC_{50}: > 12.0 mg a.i./L	0.045	< 0.0038	No
Fathead minnow (*P. promelas*)	96-hour Acute	0.1x LC_{50}: > 11.0 mg a.i./L	0.045	< 0.0041	No
	32-day Chronic ELS	NOEC: 9.5 mg a.i./L	0.045	0.0047	No
Amphibians	Acute	0.1x LC_{50}: > 11.0 mg a.i./L NOEC: 9.5 mg a.i./L	0.239	< 0.0217 0.0252	No No
Green algae (*P. subcapitata*)	96-hour Acute	0.5x E_yC_{50}: 1.65 mg a.i./L	0.045	0.0273	No
Blue-Green algae (*A. flos-aquae*)	96-hour Acute	0.5x E_yC_{50}: 0.38 mg a.i./L	0.045	0.1184	No
Diatom (*N. pelliculosa*)	96-hour Acute	0.5x E_yC_{50}: 45 mg a.i./L	0.045	0.001	No
Vascular plant (*L. gibba*)	7-day Dissolved	0.5x E_yC_{50}: 42.5 mg a.i./L	0.045	0.0011	No
Marine species					
Mysid shrimp (*A. bahia*)	96-hour Acute	0.5x LC_{50}: > 50 mg a.i./L	0.045	< 0.0008	No
Eastern oyster (*C. virginica*)	96-hour Acute	0.5x EC_{50}: > 55 mg a.i./L	0.045	< 0.0008	No

Organism	Exposure	Endpoint value with uncertainty factor, when applicable	EEC (mg a.i./L)	RQ	LOC Exceeded?
Sheepshead minnow (*C. variegatus*)	96-hour Acute	0.1x LC_{50}: > 11.0 mg a.i./L	0.045	< 0.0041	No
Diatom (*S. costatum*)	96-hour Acute	0.5x E_yC_{50}: > 47 mg a.i./L	0.045	< 0.0010	No

[a] The level of concern (LOC) is 1.0.

Table 15 Toxic substances management policy considerations – comparison of Kasugamycin to TSMP Track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Kasugamycin Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]	Soil	Half-life ≥ 182 days	Half-life: 48.9 days
	Water	Half-life ≥ 182 days	Half-life: 7 days
	Sediment	Half-life ≥ 365 days	Half-life: 156 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (< 0.013 mPa at 25°C) and Henry's Law Constant (2.44×10^{-13} atm·m^3·mole^{-1}).
Bioaccumulation[4]	Log K_{OW} ≥ 5		Log K_{OW}: < -1.96 at pH 5
	BCF ≥ 5000		Not available
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 Field data (for example,. BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Table 16 Summary of Fungicide Alternatives for the Uses Supported with Kasumin 2L Bactericide

Crop	Disease	Active ingredient and Resistance management group
Fruiting vegetables	Bacterial spot	Acibenzolar-S-methyl (P)
		Bacillus subtilis QST 713 (44)
		Copper hydroxide (M1)
	Bacterial stem canker	Copper hydroxide (M1)
		Copper oxychloride (M1)
Pome fruits	Fire blight	*Bacillus subtilis* QST 713 (NC)
		Copper oxychloride (M1)
		Pantoea agglomerans strain C9-1 (NC)
		Pantoea agglomerans strain E325 (NC)
		Pseudomonas fluorescens strain A506 (NC)
		Prohexadione calcium (P)
		Streptomycin sulphate (25)
		Tribasic Copper Sulphate (M1)
Walnut	Walnut blight	Copper oxychloride (M1)

Table 17 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Fruiting vegetables (greenhouse, field): control of bacterial speck with three applications of Kasumin 2L Bactericide at 1.2 L/ha. Minimum 7-day interval between applications.	Not supported. The disease was not present in two of the three submitted field trials. Kasumin 2L Bactericide was not used as a stand-alone treatment in the other trial.
Fruiting vegetables (greenhouse, field): control of bacterial spot with three applications of Kasumin 2L Bactericide at 1.2 L/ha. Minimum 7-day interval between applications.	Supported for **suppression**.
Fruiting vegetables (greenhouse, field): control of bacterial stem canker with three applications of Kasumin 2L Bactericide at 1.2 L/ha. Minimum 7-day interval between applications.	Supported for **suppression**.
Fruiting vegetables (greenhouse and field): For broad disease control of bacterial spot, bacterial stem canker and bacterial speck, Kasumin 2L Bactericide may be tank-mixed with Kocide.	Kasumin 2L Bactericide may be tank-mixed with Kocide DF, Kocide 101 or Kocide 2000 for control of the registered bacterial diseases on tomatoes and peppers (greenhouse seedlings for transplant, field). The most restrictive label precautions and limitations must be followed.
Pome fruits: control of fire blight with four applications at 5.0 L/ha on a 7-day interval or when conditions favour disease development.	Supported as proposed.
Walnut: control of walnut blight with four applications at 5.0 L/ha when conditions favour disease development on a minimum 14-day interval.	Supported for **suppression**.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The Canadian MRLs differ from the tolerance established in the United States (40 CFR Part 180). The USEPA is currently re-examining the tolerances. Codex MRLs are not currently established for kasugamycin on any commodities.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	United States* (ppm)	Codex** (ppm)
Fruiting vegetables (CG 8-09)	0.1	0.04	Not reviewed by Codex
Pome fruits (CG 11-09)	0.2	Apple 0.05	
Walnuts	0.04	--	

* USEPA tolerances established in 2005.

** Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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